Aging Phenotypes and their epigenetic basis

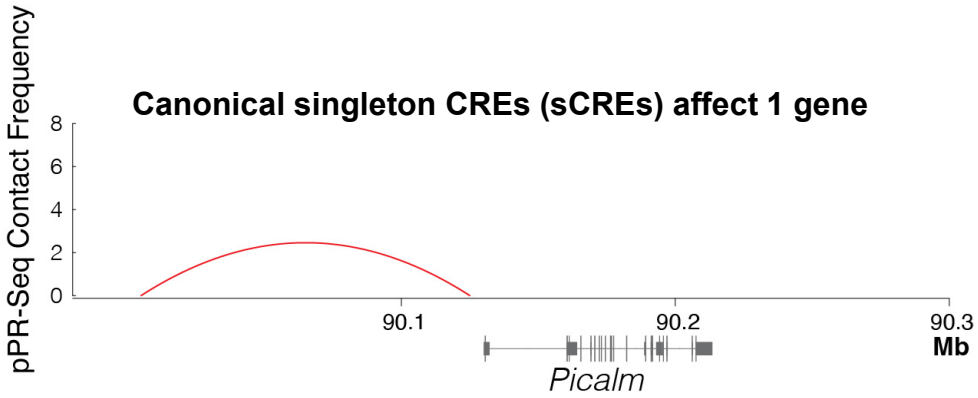
Christopher Gregg

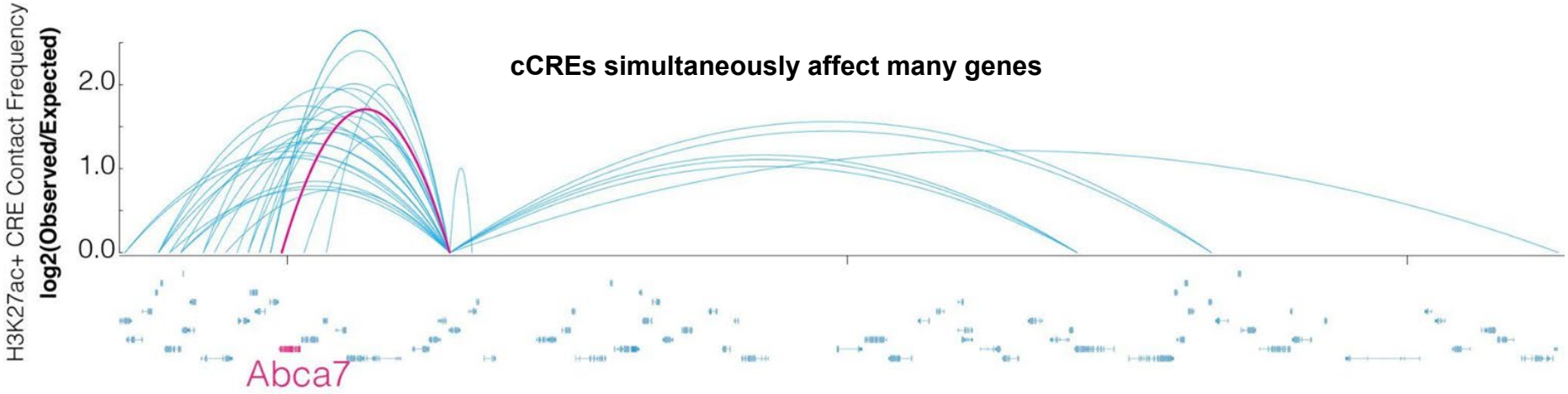
Departments of Neurobiology and Human Genetics

CONFLICT OF INTEREST: Chris Gregg is a co-founder and has equity in Storyline Health Inc.

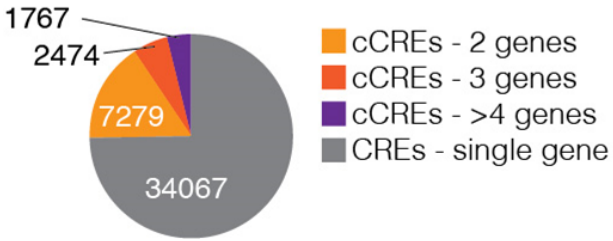
Identification of coordinator cis-regulatory elements (cCREs) in the mouse hypothalamus

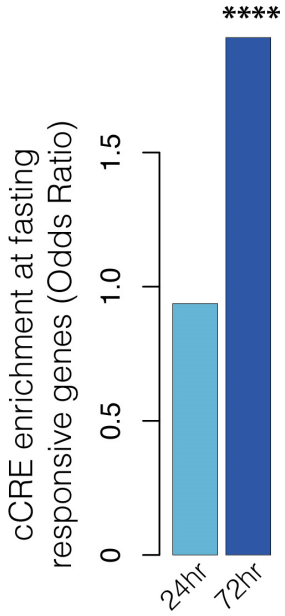
Elliott Ferris
Susan Steinwand
Zia L'Ecuyer

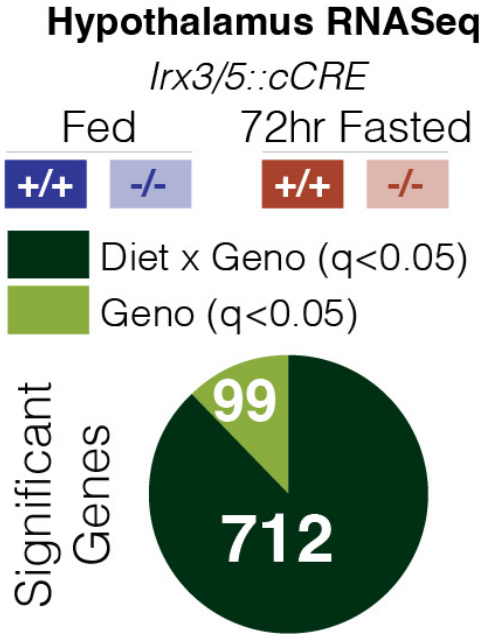




cCREs play important roles in controlling metabolic responses to starvation







cCREs - critical interfaces between metabolism, gene expression and ADRDs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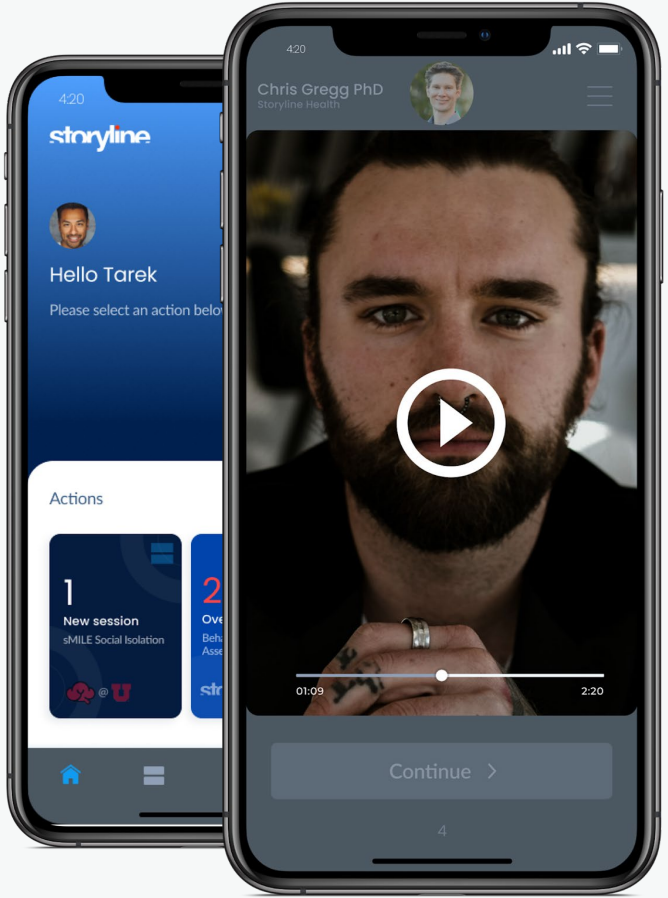
Storyline Interactions



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Pupil Dilation
Eye Tracking
Head Movement
Blood Flow
Respiration
Response Time
Micro-Expressions
Cognitive Load
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Temperature Change
Articulation

Speech

Word Choice
Sentence Structure
Personality Traits
Speech Patterns
Education Level
Engagement
Vocabulary
Time Stamping
Utterances
Sentiment
Thought Patterns
Frequency
Complexity
Outlook

Audio

Vocal Micro-Tremors
Pitch & Tone Changes
Pronunciation
Valence
Stress

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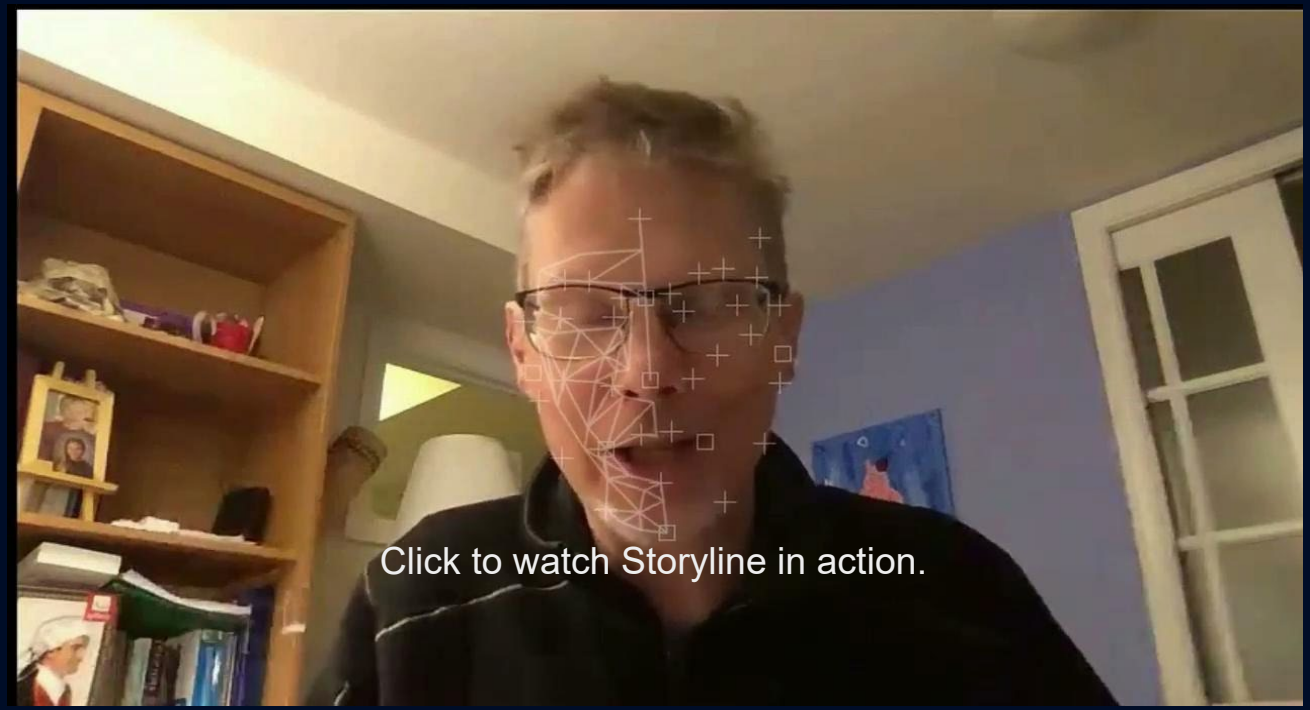
1 million times the data resolution of EHR records



Behavioral Topology: An ever increasing number of behavioral features finally provides the data resolution necessary to reveal the behavioral expression of the underlying biology.

Our Scientists

Dr. Hilary Coon PhD (Psychiatry and Epidemiology, University of Utah)

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Dr. Deborah Neklason PhD (Utah Genome Project, University of Utah)

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Dr. Tiffany Love PhD (Psychiatry, University of Utah)

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Dr. Jamie Brant MD (Oncology, Intermountain Healthcare)

Dr. Sean Gregg MD (Surgery, University of Calgary)

Dr. Chad Ball MD (Surgical Oncology, University of Calgary)

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Dr. Carlo Maley (Cancer research, Arizona State University)

Dr. Sandy Anderson (Cancer research, Moffitt Cancer Center)

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Dr. Eduardo Zarate MD (University of Utah, Gastroenterology, Hepatology)

Dr. Eric Goldstein MD (University of Utah, Vascular Neurology)

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Utah Genome Project

NYSCF
The New York Stem Cell Foundation

Intermountain Healthcare

The University of Utah School of Medicine

ASU Arizona State University

PEEL THERAPEUTICS

UNIVERSITY OF CALGARY

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

UCSF
University of California San Francisco

Mount Sinai

23andMe

Prolific

HUMAN API

storyline

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Christopher Gregg
Departments of Neurobiology and Human Genetics

CONFLICT OF INTEREST: Chris Gregg is a co-founder and has equity in Storyline Health Inc.

Microtubule stabilization as a therapeutic strategy for neurodegenerative conditions

DONNA J. CROSS, PHD

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

Introduction

Axonal transport decline and cytoskeletal abnormalities in Alzheimer's disease and other neurodegenerative conditions

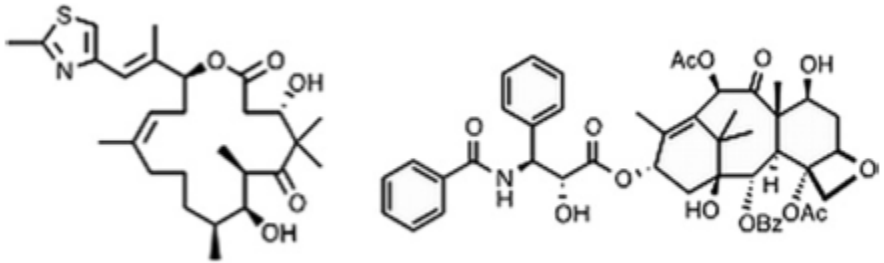
- In vivo MEMRI of olfactory tract in aging and AD Tg (APPswe/PS1) (Cross,et. al., 2008, Minoshima and Cross, 2008)
- DTI and FDG-PET in human MCI (Cross,et. al., 2013)
- Cytoskeletal injury and axonal transport disruption is a feature of traumatic brain injury and may represent the common pathway for TBI and an increased risk of future neurodegenerative disease

Hypothesis: Intranasal administration of *paclitaxel*, a microtubule-stabilizing drug would improve axonal transport in triple transgenic AD mice (3xTg-AD)

Rationale

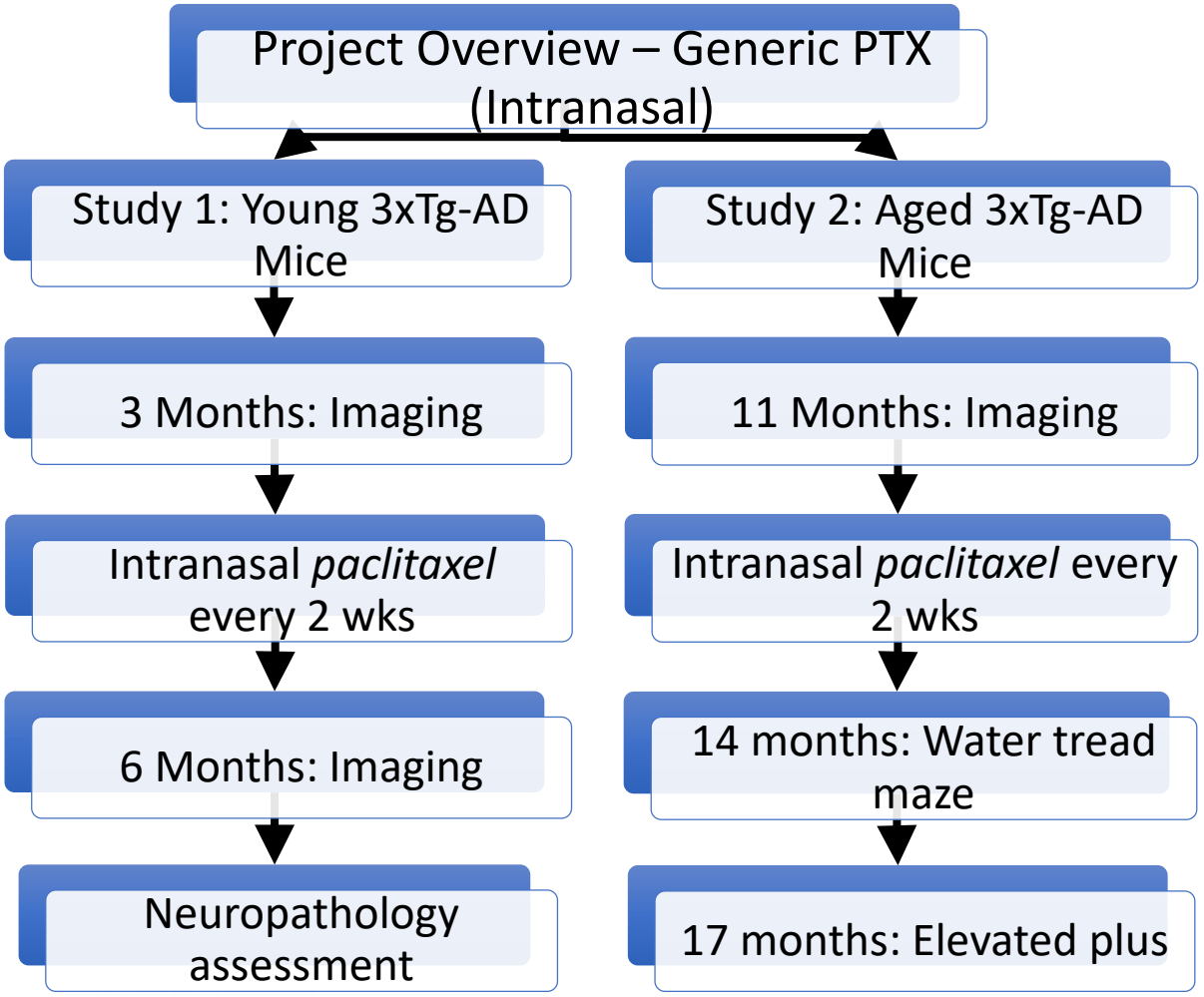
- Microtubule-stabilizing cancer drugs inhibit cellular mitosis by stabilizing the GDP-bound tubulin in microtubules thereby preventing depolymerization
- In neurons, microtubules are organized into fibers that make up the cytoskeleton which supports axonal transport and neuronal homeostatic processes.
- Evidence indicates a neurotherapeutic effects after neuronal injury (Adlard, et. al, *Acta Neuropath* 2000, Hellal, et. al. *Science*, 2011)
- These drugs have been suggested as therapies for neurodegenerative disease because they can functionally replace tau protein, which plays a critical role in stabilizing the cytoskeleton

Cytoskeletal stabilizing therapeutics



Cytoskeletal stabilizing therapeutics in TBI and AD

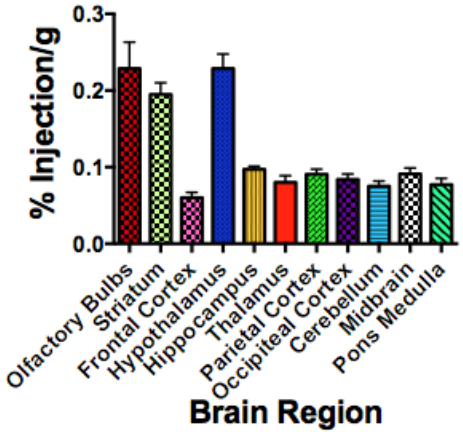
- "Cytoskeletal stabilization as a therapeutic strategy following traumatic brain injury" (Cross et al, 2013 SfN 2013 abstract)
- *"Epothilone D* Improves Microtubule Density, Axonal Integrity, and Cognition in a Transgenic Mouse Model of Tauopathy" (Brunden et. al., *J. of Neuroscience* 2010)
- *Epothilone D* good BBB permeability, *paclitaxel* low BBB permeability
- However, *paclitaxel* has been used for more than 20 years in cancer therapy and is VERY well-characterized

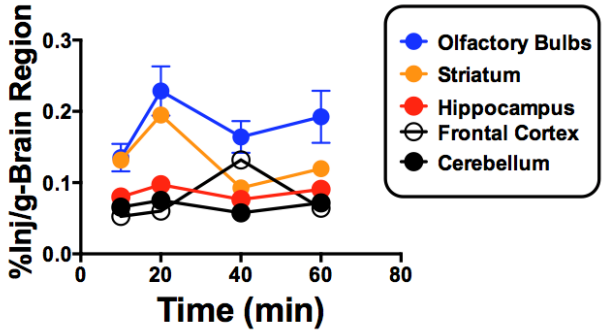

Project Overview – Generic PTX (Intranasal)
Study 1: Young 3xTg-AD Mice
3 Months: Imaging
Intranasal *paclitaxel* every 2 wks
6 Months: Imaging
Neuropathology assessment
Study 2: Aged 3xTg-AD Mice
11 Months: Imaging
Intranasal *paclitaxel* every 2 wks
14 months: Water tread maze
17 months: Elevated plus

Intranasal Administration

1. Allows non-invasive access of therapeutic to the brain
2. Increased brain/blood ratio for therapeutic: more brain-specific targeted delivery for long term dosing (10-20 years for AD)
3. Olfactory tract and connected regions have been shown to be affected severely in Alzheimer's disease
4. Other AD therapeutics have shown promise with intranasal delivery (i.e. intranasal insulin, Craft, et. al. *Arch Neurol* 2011)

Brain distribution of *paclitaxel* after intranasal administration



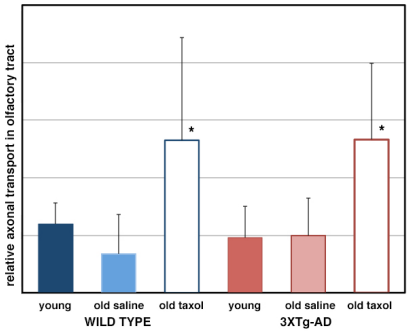


- Results are expressed as the percent of the administered dose taken up by a gram of brain region.
- Time activity curve compares 5 brain regions. Although there are regional differences, fairly stable over time.
- The classic pattern of high olfactory bulb is shown, but high striatum is unique.

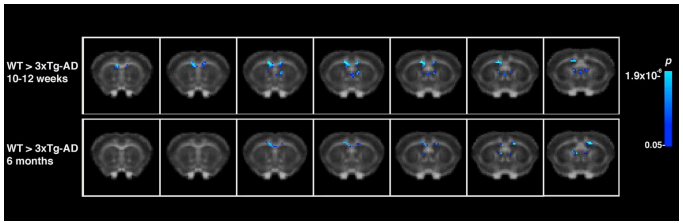
Cross et al, J of Alz Dis, 2019

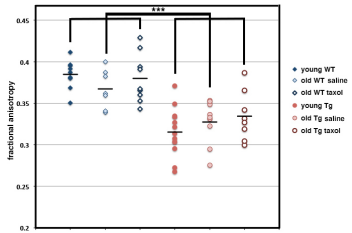
Imaging

- Manganese Enhanced MRI (MEMRI) of axonal transport
- Diffusion Tensor Imaging of white matter integrity (fractional anisotropy(FA) maps)



MEMRI

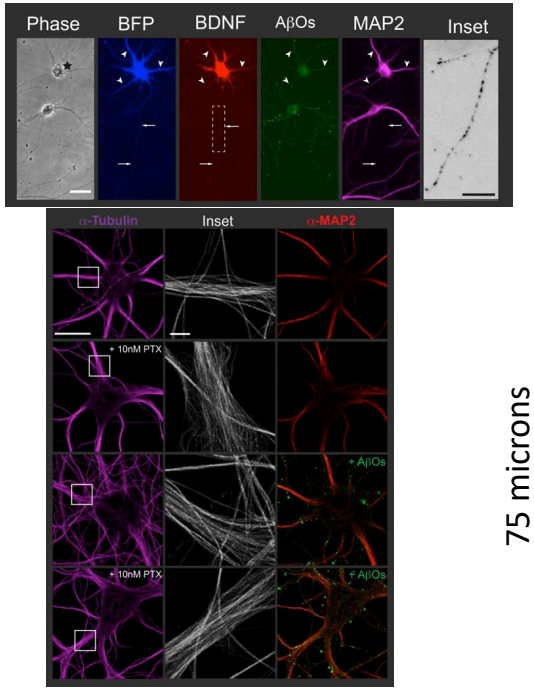




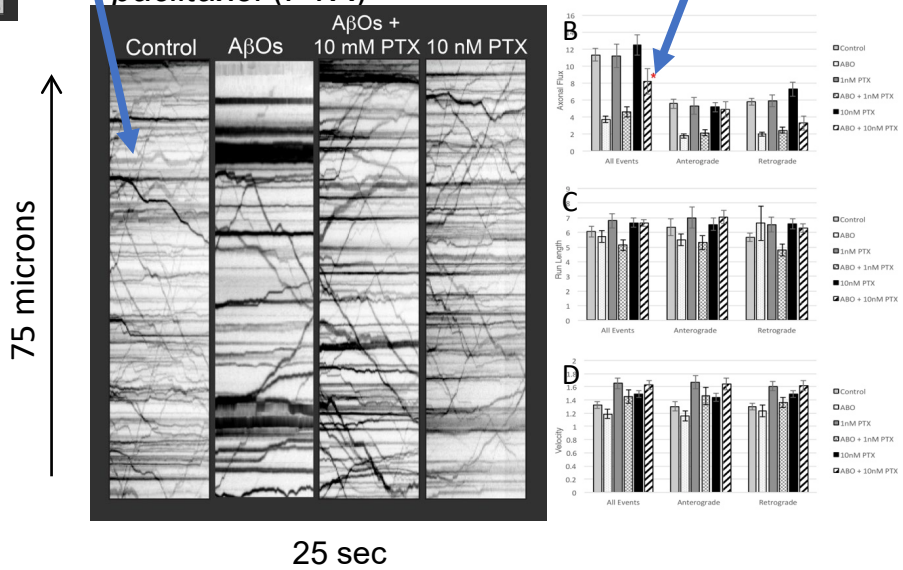
FA

Cross et al, J of Alz Dis, 2021

Low concentration (10nM) *paclitaxel* increased transport in cultured hippocampal neurons treated with Aß oligomers

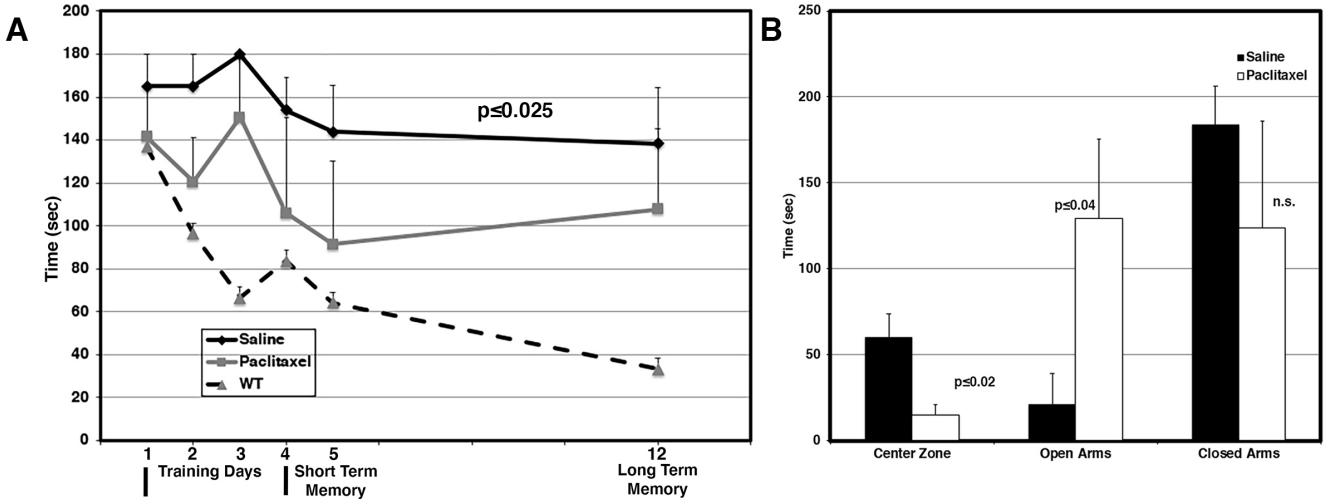


- Expression of soluble BFP and BDNF-RFP in an ABO-treated neuron
- Positive Slope is anterograde transport
- Vesicle flux in ABOs increases with 10 NM *paclitaxel* (PTX)



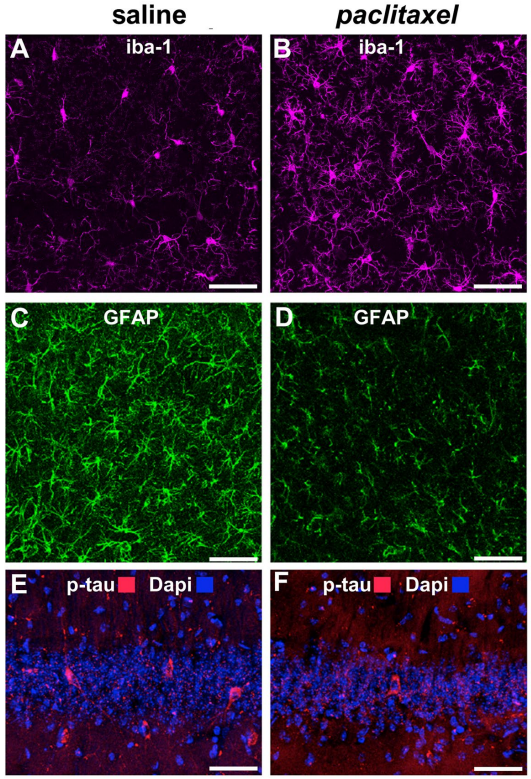
Cross et al, J of Alz Dis, 2021

Water Tread Maze shows improved cognition and elevated plus maze shows reduced anxiety in aged 3xTg-AD mice after intranasal *paclitaxel*



Cross et al, J of Alz Dis, 2021

Paclitaxel alters neuronal phospho-tau levels and neuroinflammatory response in 3xTg-AD



Cross et al, J of Alz Dis, 2021

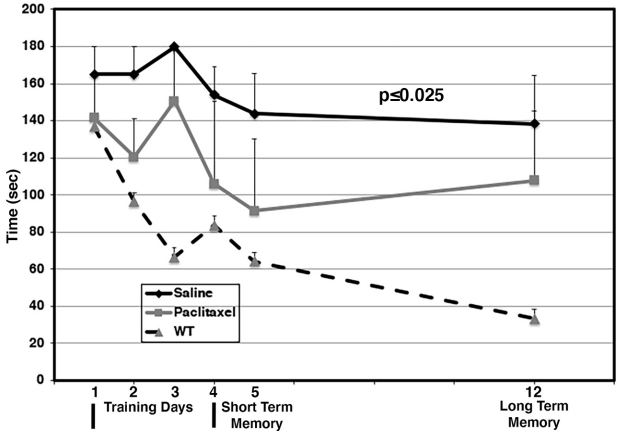
NEXT PHASE:
Backbone Degradable Polymer-drug Conjugate for Treatment of AD

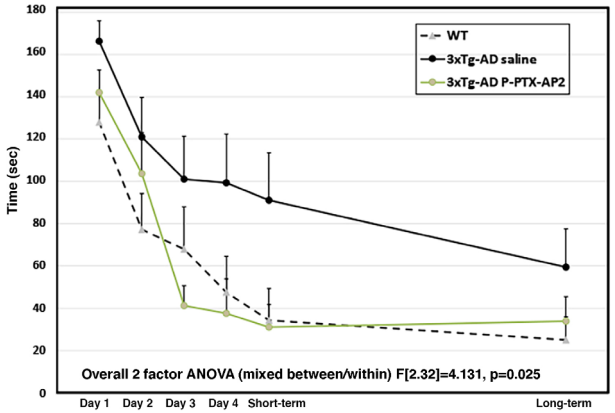
COLLABORATORS (College of Pharmacy)

Dr. Jindrich Kopeček
Dr. Jiyuan Yang

Funding: Alzheimer's Association Research Grant

Water Tread Maze indicates improved efficacy with co-polymer peptide PTX conjugate over intranasal generic PTX in AGED 3xTg-AD mice





Generic PTX (intranasal)

2P-PTX-AP2 (IV administration)

Neuroimaging and Biotechnology Lab

Department of Radiology and Imaging Sciences

University of Utah, Salt Lake City, UT, USA

- Donna J. Cross, PhD
- Yoshimi Anzai, MD, MPH
- Maxwell Monson
- Students: Thomas Blake, Ashton Jensen, Raghad Aljassimi

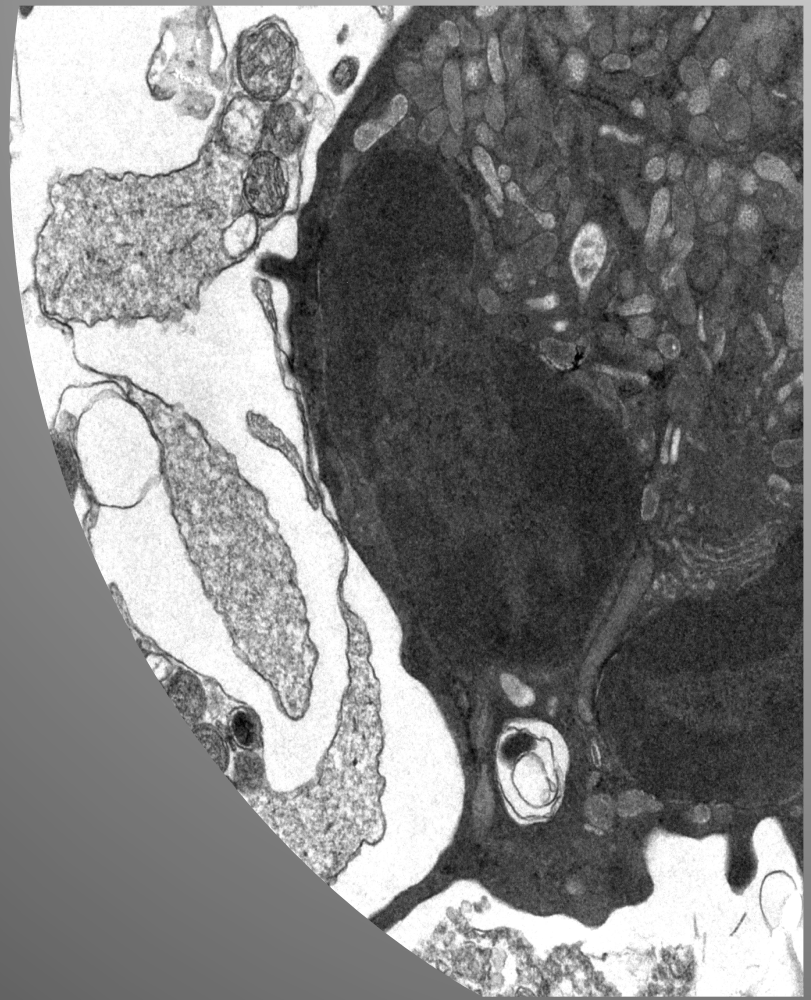
Satoshi Minoshima, MD, PhD

- Collaborators: University of Utah
- Dr. Jindrich Kopeček
- Dr. Jiyuan Yang
- Collaborators: Puget Sound VA, Seattle WA
- Elaine R. Peskind, MD
- William A. Banks, MD

David G. Cook, PhD

James A. Meabon, PhD

Neutrophils and Neurological Outcomes in Stroke



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Assistant Professor of Medicine

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Division of General Medicine

University of Utah Molecular Medicine Program

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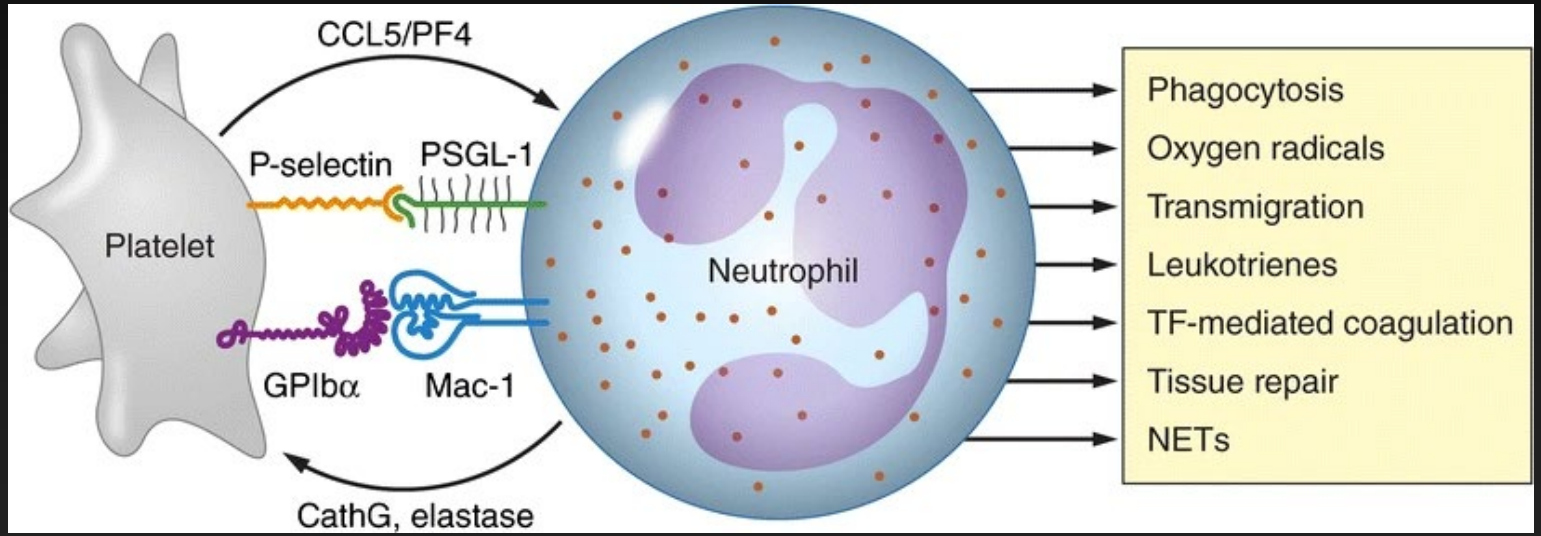
HEALTH

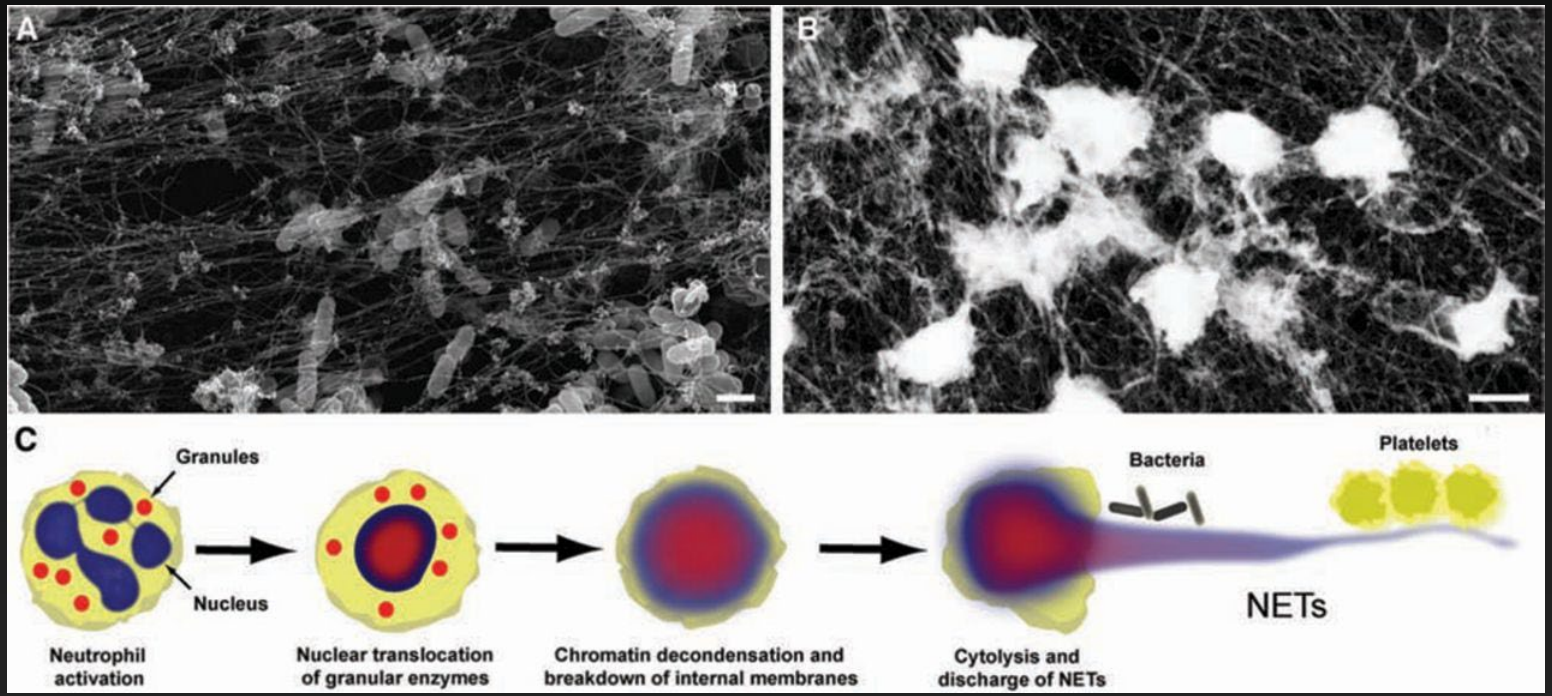
UNIVERSITY OF UTAH

Platelets Interact with Other Cells



Lisman et al Cell and Tissue Research 2017

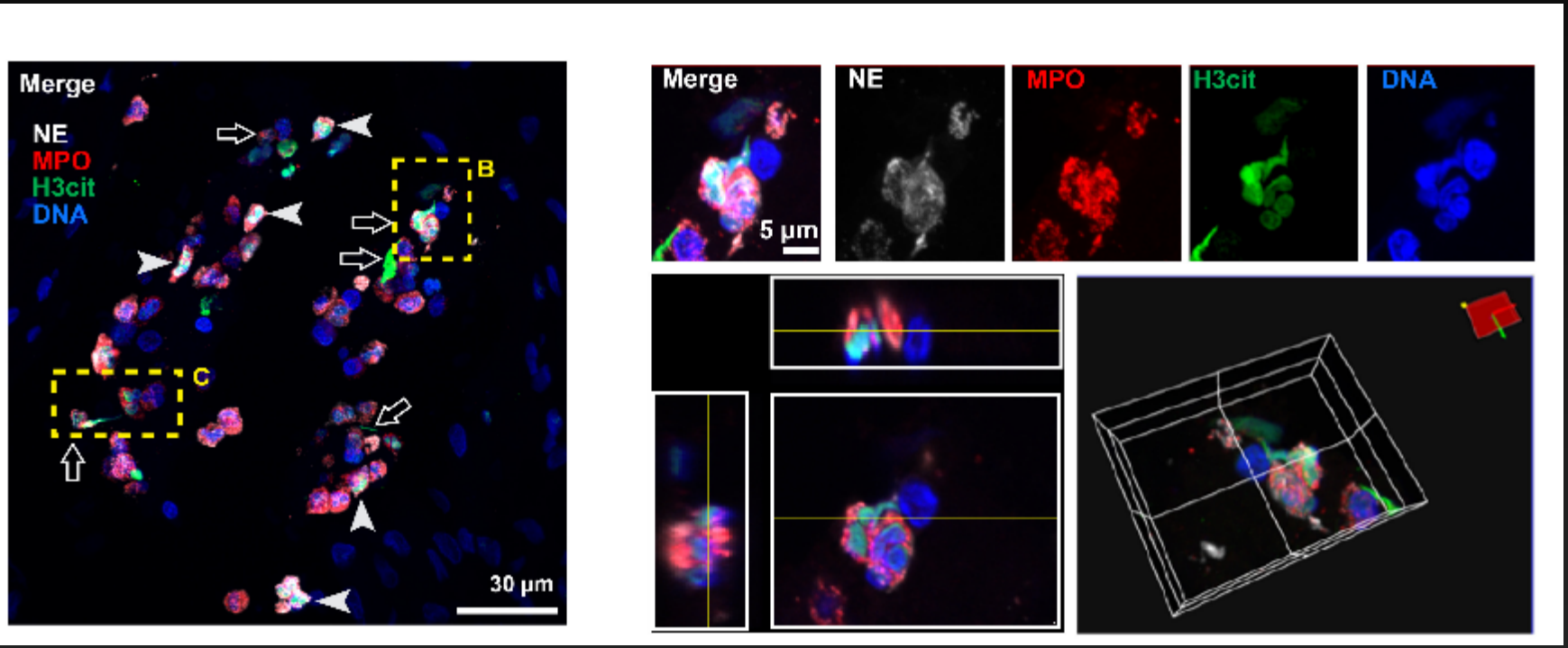
Neutrophil Extracellular Traps enhance Thrombosis



Fuchs TA et al. ATVB (2012)

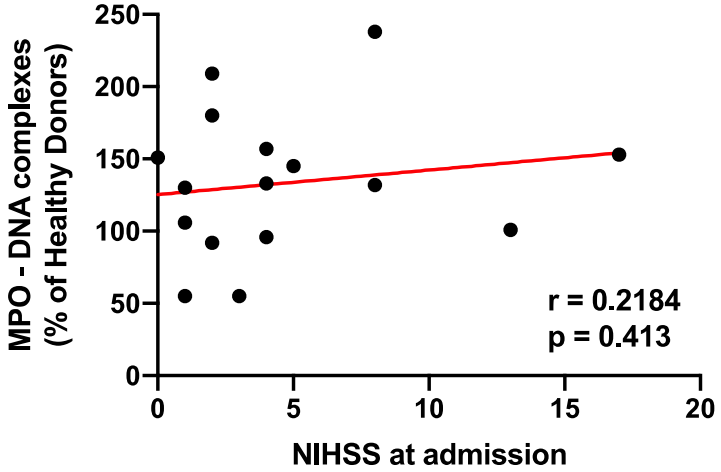
Platelet-Neutrophil interactions induce the formation of neutrophil extracellular traps contributing to immunothrombosis & neurotoxicity.

NETs are Present in the Brains of Human Stroke Patients

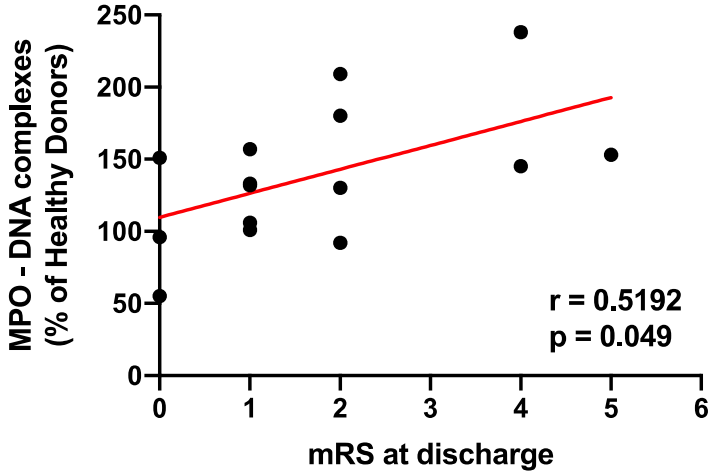


Denorme et al *JCI 2022* in Press

MPO-DNA complexes correlate with Stroke Outcomes



Stroke Severity

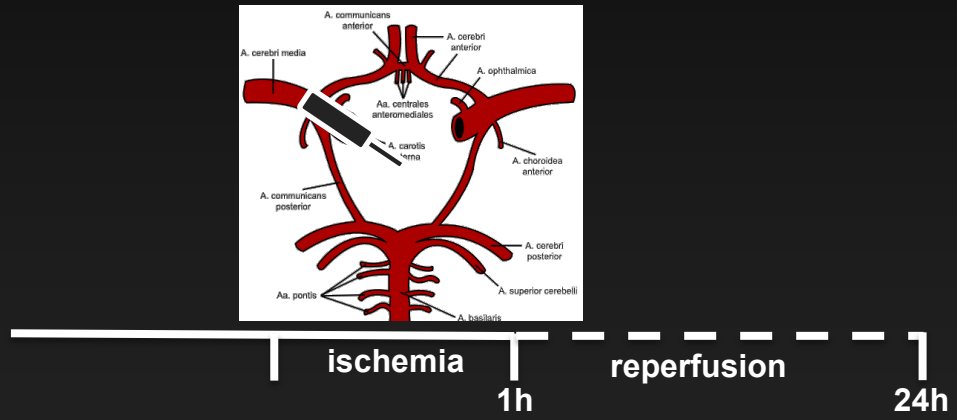


Disability Score

Unpublished

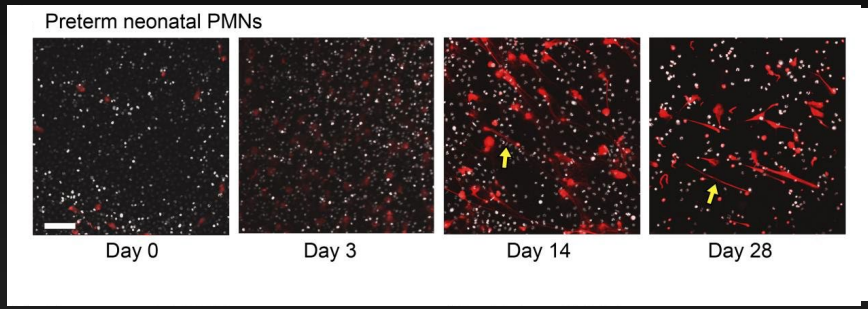
Denorme et al *JCI 2022* in Press

Does NET Inhibition Confer Protection from Ischemic Stroke Brain Injury?

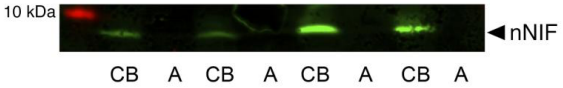


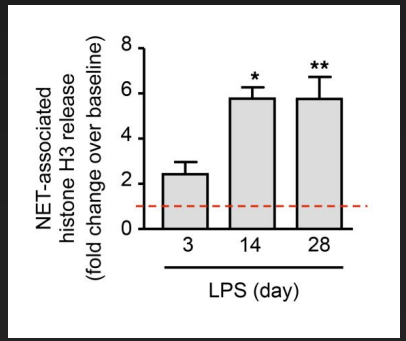
Denorme et al *JCI 2022* in press

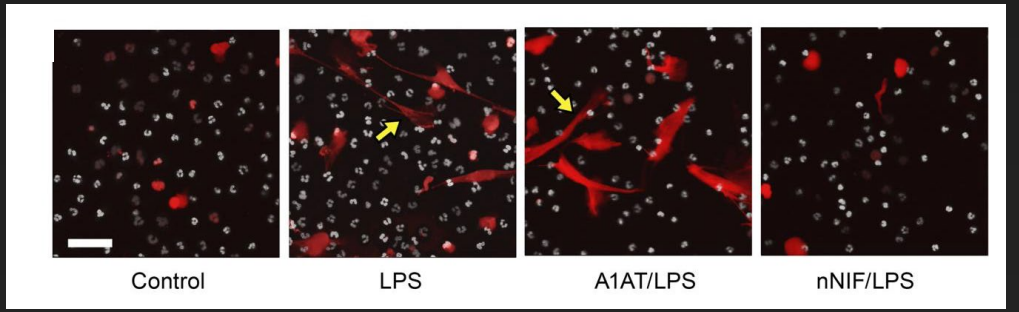
Novel ways to inhibit NET formation



nNIF	NH_2 - ----------KFNKPFVFLMIEQNTKSPLFMGKVVNPTQ_-COOH
CRISPP	NH_2 - _M_IPPEVKFNKPFVFLMIDQNTKVPLFMGK----------COOH
C-terminus A1AT	NH_2 - PMSIPPEVKFNKPFVFLMIEQNTKSPLFMGKVVNPTQK-COOH

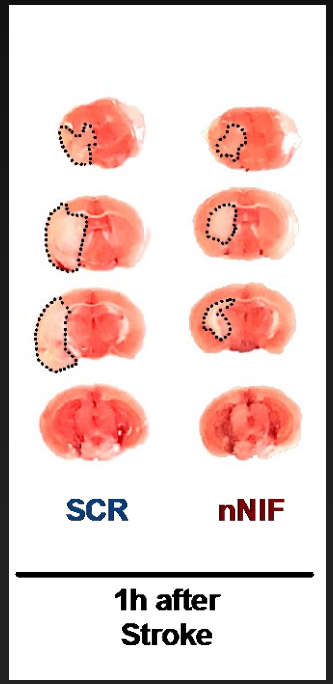


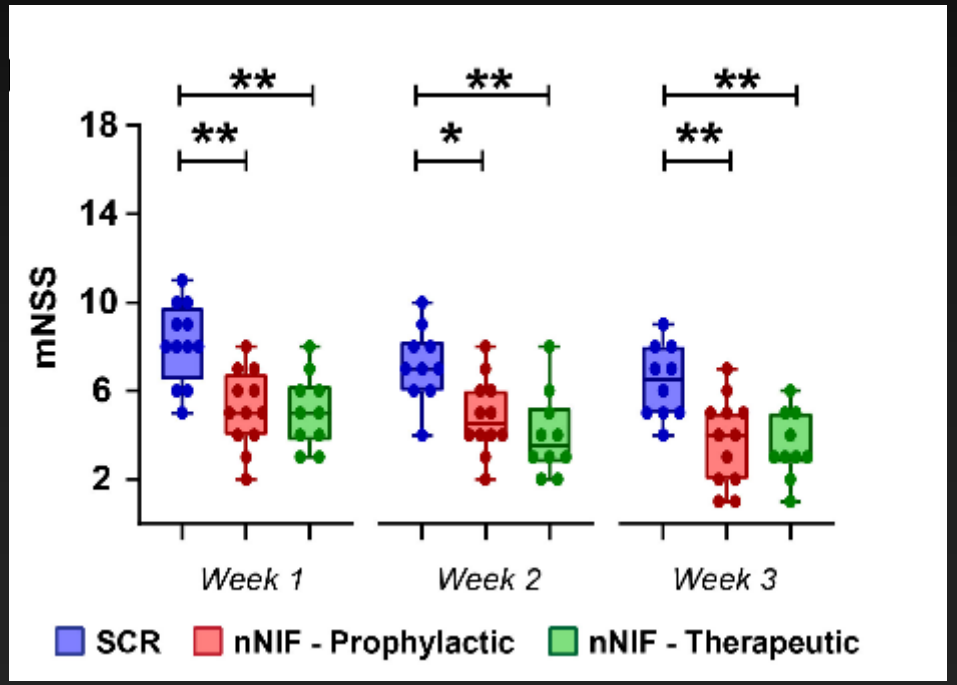




Yost et al 2016 JCI

NET Inhibition Improves Long Term Motor and Neurological Function After Ischemic Stroke





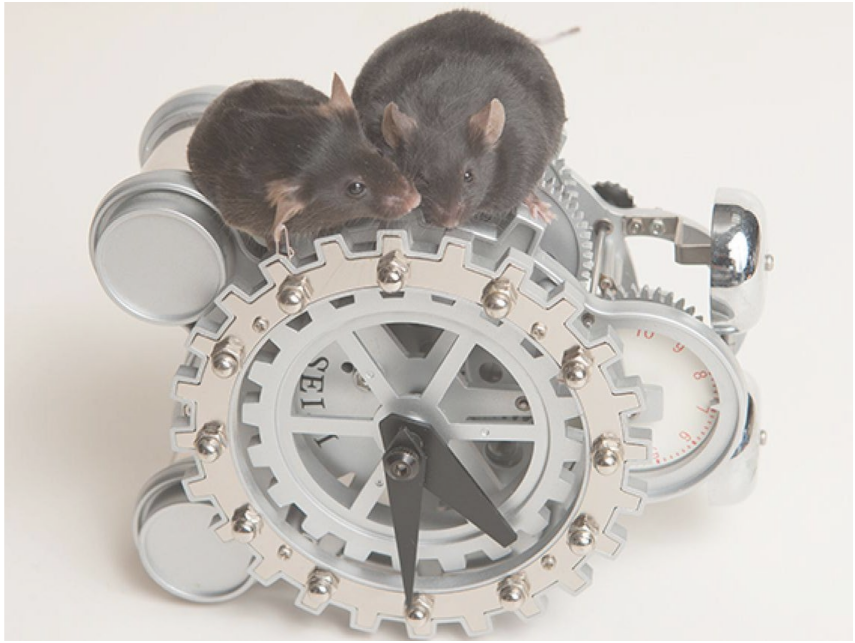
Denorme et al *JCI 2022* in press

Areas for Collaboration

- Animal models of ischemic stroke – capable of looking at long-term outcomes
- Animal models of infection – capable of looking at long-term outcomes

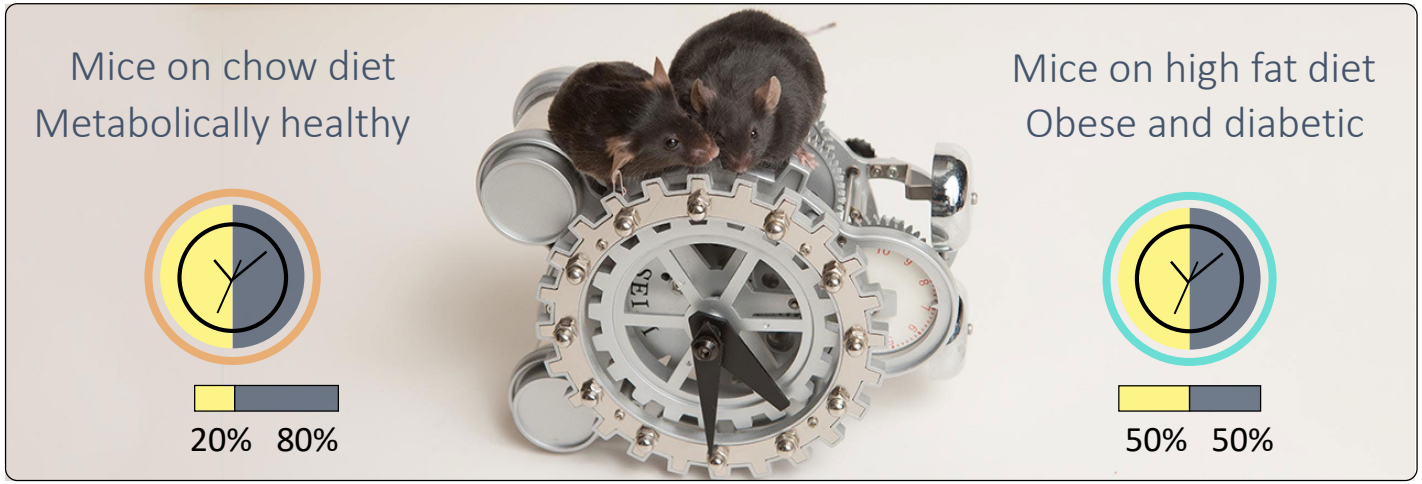
- Phenotyping
  - neutrophil activation and NET release in the context of aging and neurological outcomes
  - platelets activation in the context of aging and neurological outcomes

Time to live healthier and longer ?
The tale of mice on Time-Restricted Feeding



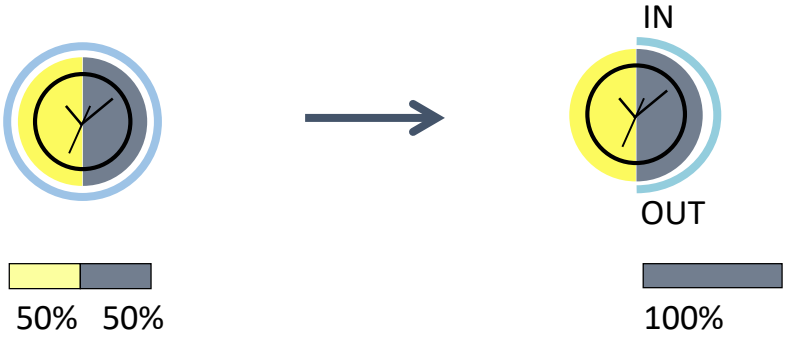
Amandine Chaix, Ph.D., NUIP, COA Retreat, May 25 2022

Role of temporal eating patterns in metabolic homeostasis?



- Altered eating patterns in DIO mice
- Is food consumption during the rest phase involved in the obesity and diabetes phenotype ?

Is food consumption during the rest phase involved in the obesity and diabetes phenotype ?



Time-restricted feeding:

Consolidation of caloric intake to the dark/active phase for 8-10 hours

Cell Metabolism
Article

Time-Restricted Feeding without Reducing Caloric Intake Prevents Metabolic Diseases in Mice Fed a High-Fat Diet

Megumi Hatori,[1,4] Christopher Vollmers,[1,4] Amir Zarrinpar,[1,2,4] Luciano DiTacchio,[1,4] Eric A. Bushong,[3] Shubhroz Gill,[1] Mathias Leblanc,[1] Amandine Chaix,[1] Matthew Joens,[1] James A.J. Fitzpatrick,[1] Mark H. Ellisman,[3] and Satchidananda Panda[1,*]
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DOI 10.1016/j.cmet.2012.04.019

Cell Reports
CellPress
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Report

Sex- and age-dependent outcomes of 9-hour time-restricted feeding of a Western high-fat high-sucrose diet in C57BL/6J mice

Amandine Chaix,[1,2,*] Shaunak Deota,[1] Raghav Bhardwaj,[1] Terry Lin,[1] and Satchidananda Panda[1,3,*]
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*Correspondence: amandine.chaix@utah.edu (A.C.), satchin@salk.edu (S.P.)
https://doi.org/10.1016/j.celrep.2021.109543

Cell Metabolism
Article
CellPress

Time-Restricted Feeding Is a Preventative and Therapeutic Intervention against Diverse Nutritional Challenges

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Cell Metabolism
Article
CellPress

Time-Restricted Feeding Prevents Obesity and Metabolic Syndrome in Mice Lacking a Circadian Clock

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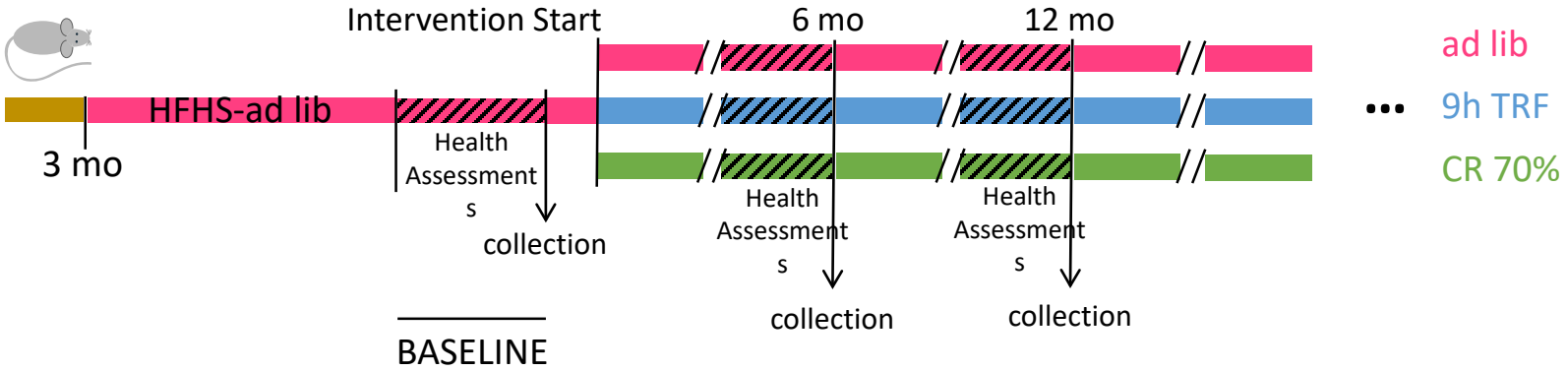
https://doi.org/10.1016/j.cmet.2018.08.004

Ongoing research

- Can TRF extend healthy life in preclinical animal models ?
- Can TRF delay the onset or progression of Alzheimer Disease ?

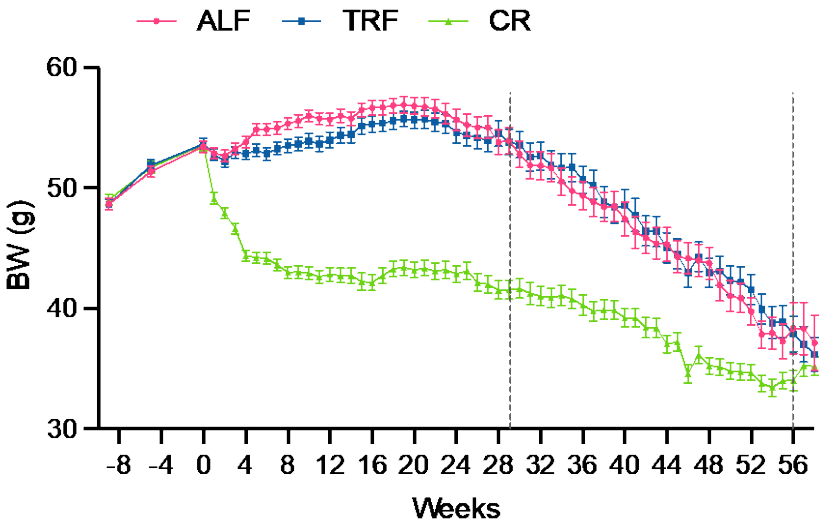
Healthspan and Lifespan Benefits of TRF under western high-fat high-sucrose nutrition

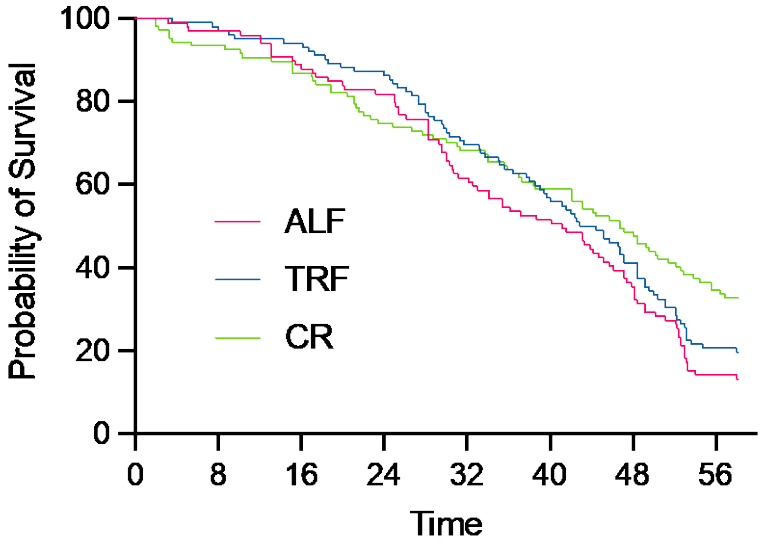
Healthspan: Cardiometabolic & Cognitive functions

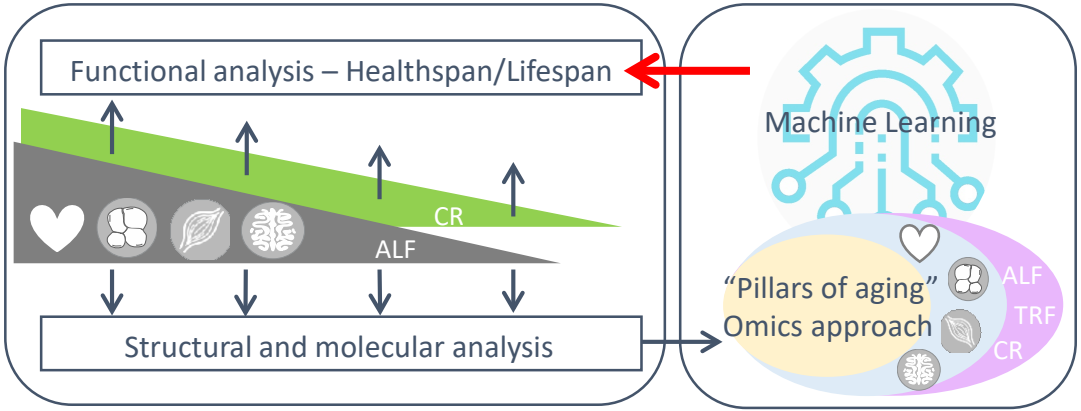


Cardiometabolic parameters, Performance, Learning & Memory ….

Body Weight & Survival







Identify pathways critically involved in
healthspan & longevity
in preclinical models

Testing our findings in humans

Targeting Protein Degradation Pathways to Maintain Proteostasis During Aging

Rajeshwary Ghosh, PhD

Research Assistant Professor

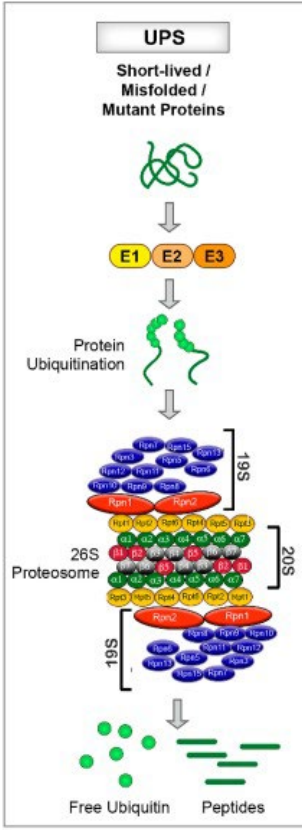
Nutrition and Integrative Physiology

University of Utah

15th Annual Research Retreat
Center on Aging
University of Utah
May, 2022

THE UNIVERSITY OF UTAH

Protein Homeostasis (Proteostasis) is Disrupted in Aging Related Disorders



Ghosh et al. Cells 2020 Apr 10;9(4):933.

Mutant/Misfolded Protein Accumulation are Causal for Various Age-related Disorders

Neurodegenerative diseases :

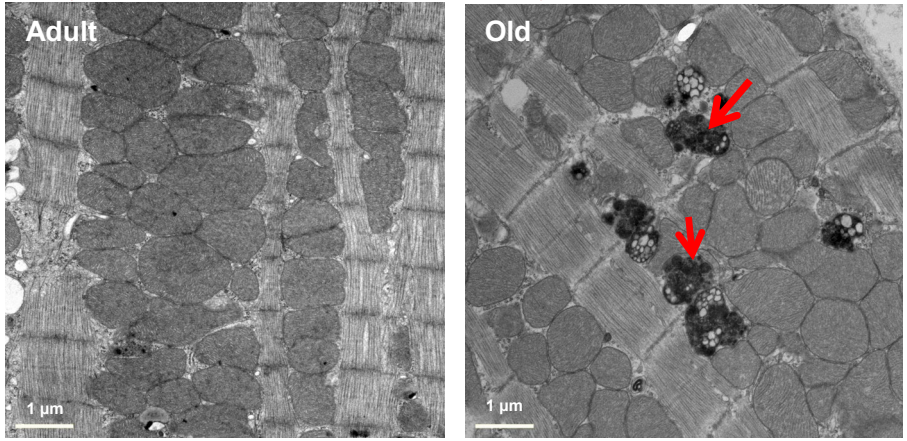
Huntington’s Disease
Alzheimer's disease
Parkinson’s Disease
Amyotrophic lateral sclerosis (ALS)

Cardiovascular Diseases:

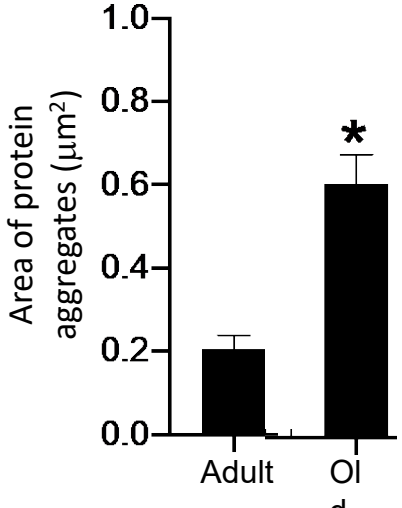
Amyloid cardiomyopathy
Desmin related Cardiomyopathy (CryABR120G)
Mutations in various structural proteins, titin (TTN), lamin A/C (LMNA), β-myosin heavy chain (MYH7), and cardiac troponin T (TNNT2)..

Accumulation of protein aggregates in the hearts of in the old (24 month) mice v/s adult (5 month) mice

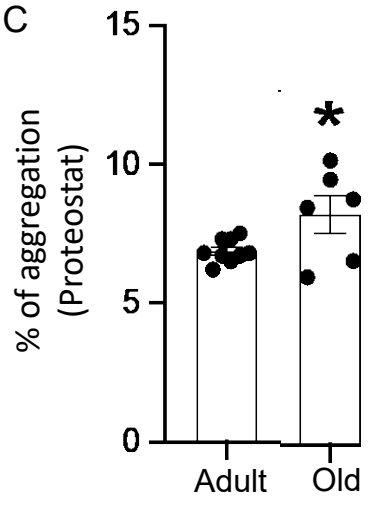
A



B



C

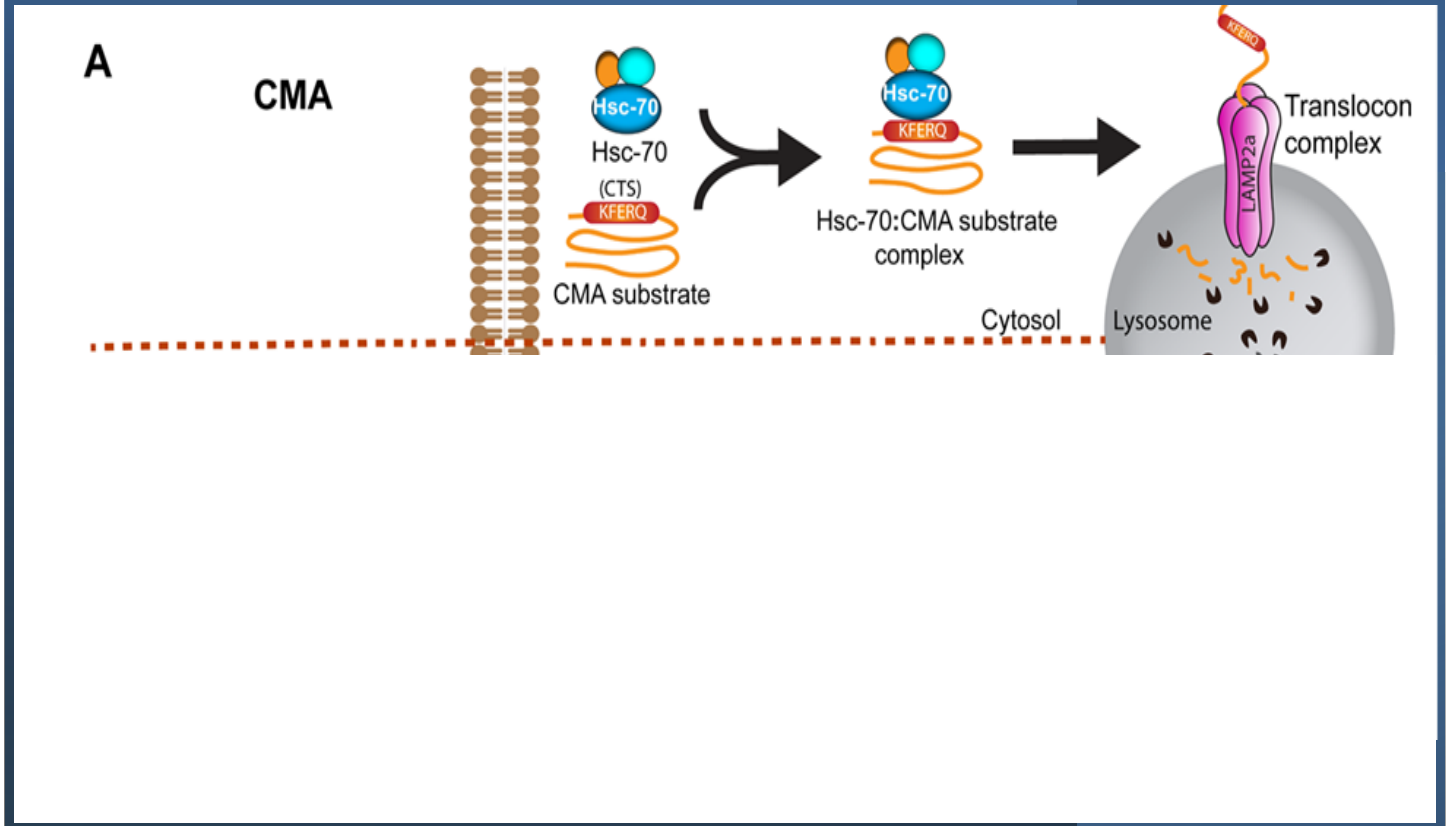


Cho et al. Aging Cell. 2021

GOAL 1: Develop a Novel Technology to Specifically Clear Mutant Proteins

RTW Charitable Foundation for Rare Disease Research

Schematic of CMA-Adeno-Associated Viral Technology (CTAVT) to Clear Mutant Protein in the Heart

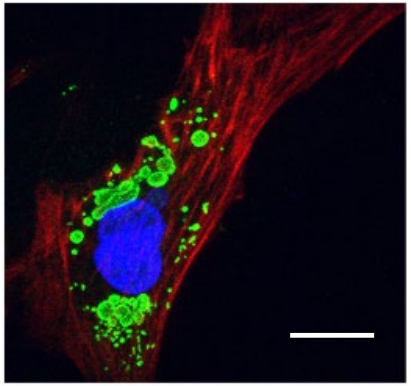


CTAVT to target CryAB-R120G mutant protein in the Heart

CrystallinAB-WT

CRYAB, a small heat shock protein

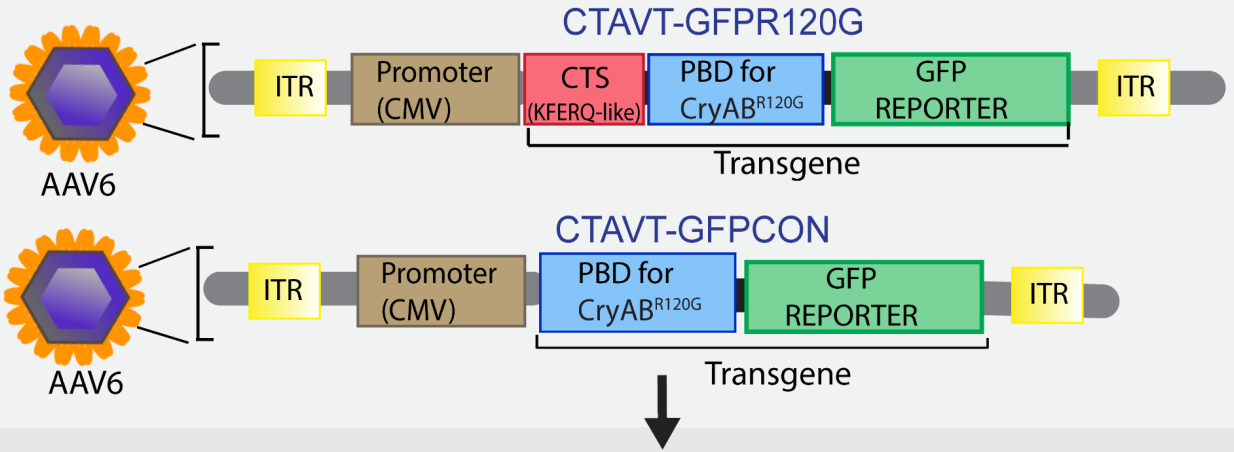
CrystallinAB-R120G



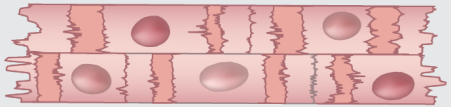
Missense mutation (R120G) in Crystallin AB, causes the protein to form insoluble aggregates in the heart, skeletal muscles and eye

Schematic of the Workflow for Generating and Testing CTAVT

AIM 1- Design CTAVT for mutant CryABR120G



AIM 2- Determine if CTAVTs can eliminate CryABR120G mutant protein in human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CM)



hiPSC-CM expressing
CryABR120G or CryABWT

SUMMARY

CTAVT as a Potential Tool to Target Mutant Proteins in the Aging Brain

Huntington’s Disease: Target mutant huntingtin (mHTT) protein

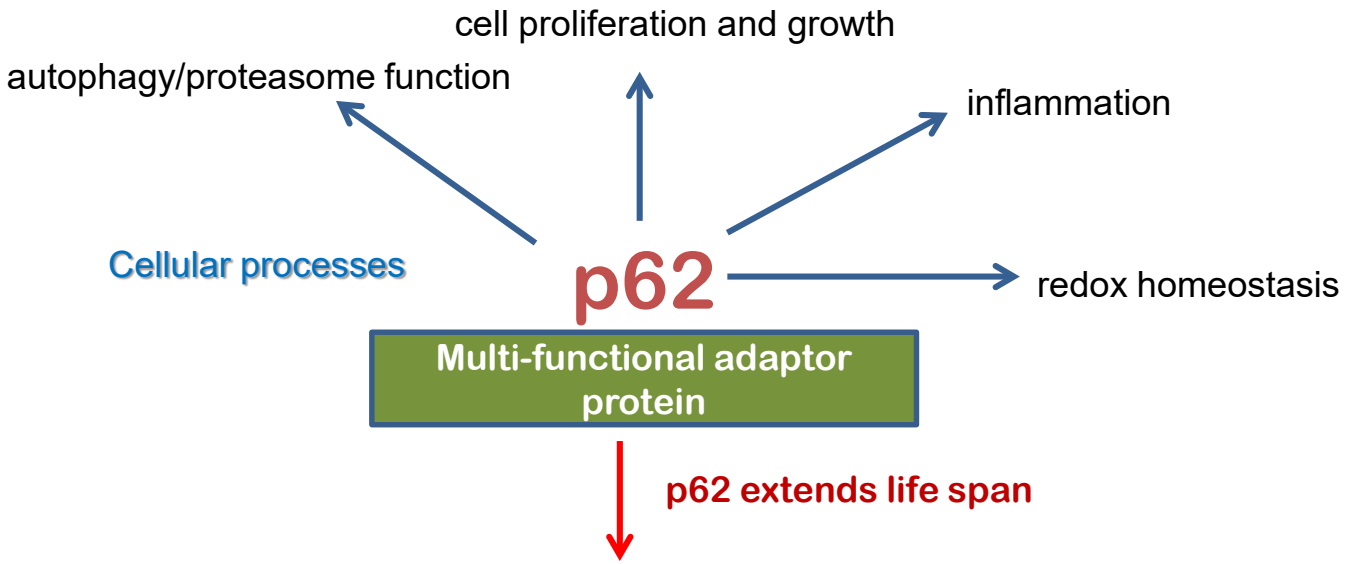
Alzheimer's disease: Target: Amyloid precursor protein (APP).
Presenilin 1 (PSEN1) or
Presenilin 2 (PSEN2)

Parkinson’s Disease: LRRK2, PARK7, PINK1, PRKN, or SNCA

GOAL 2: Target Adaptor Proteins to Ameliorate Cardiac Pathology During Aging

American Heart Association Career Development Award

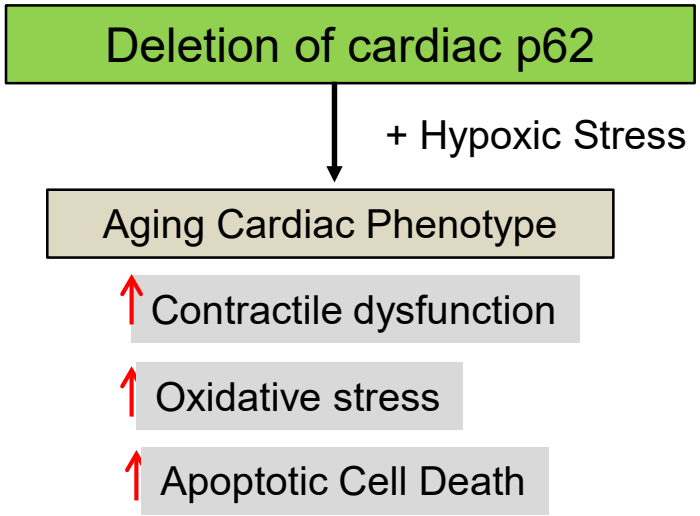
p62 participates in multiple cellular processes



In C elegans, p62 overexpression was sufficient to induce autophagy and enhance longevity and proteostasis. *Kumatsa et al., Nat. Comm. 2019*

P62 KO mice have reduced lifespan (by 34%), show premature signs of aging and increased oxidative stress, as well as increased mitochondrial damage and dysfunction. *Kwon J, et al. EMBO Rep. 2012.*

SUMMARY



P62 is necessary for maintaining normal cardiac function during aging

Ghosh et al. Unpublished

Pepper Center Core and Collaboration

1) Clinical Core:

Stimulate translation of CTAVT's approach in clearing mutant proteins in cells/mice to humans.

Collaboration with other institutions regarding CTAVT technology, and gene therapy in older individuals.

Explore **biorepository** options to procure aging samples for determining the status of protein homeostasis.

2) Data and Biomarker Core:
Receive advice on the design and conduct of clinical research pertaining to the potential of testing CTAVT intervention in older adults.

THANK YOU

- # Acknowledgments

Dr. Dave Symons (NUIP, UU)
Dr. Sihem Boudina (NUIP, UU)
Dr. Michael Kay (Biochemistry, UU)
Dr. Kent Lai (Pathology, UU)

COH Seed Grant 2020 Awarded to RG
RTW Rare Disease Funding to RG
American Heart Association CDA to RG

Defining the contribution from endothelial cell metabolism to aging-associated cerebrovascular complications in the absence and presence of ischemic stroke

J. David Symons
Center on Aging Retreat
May 25, 2022

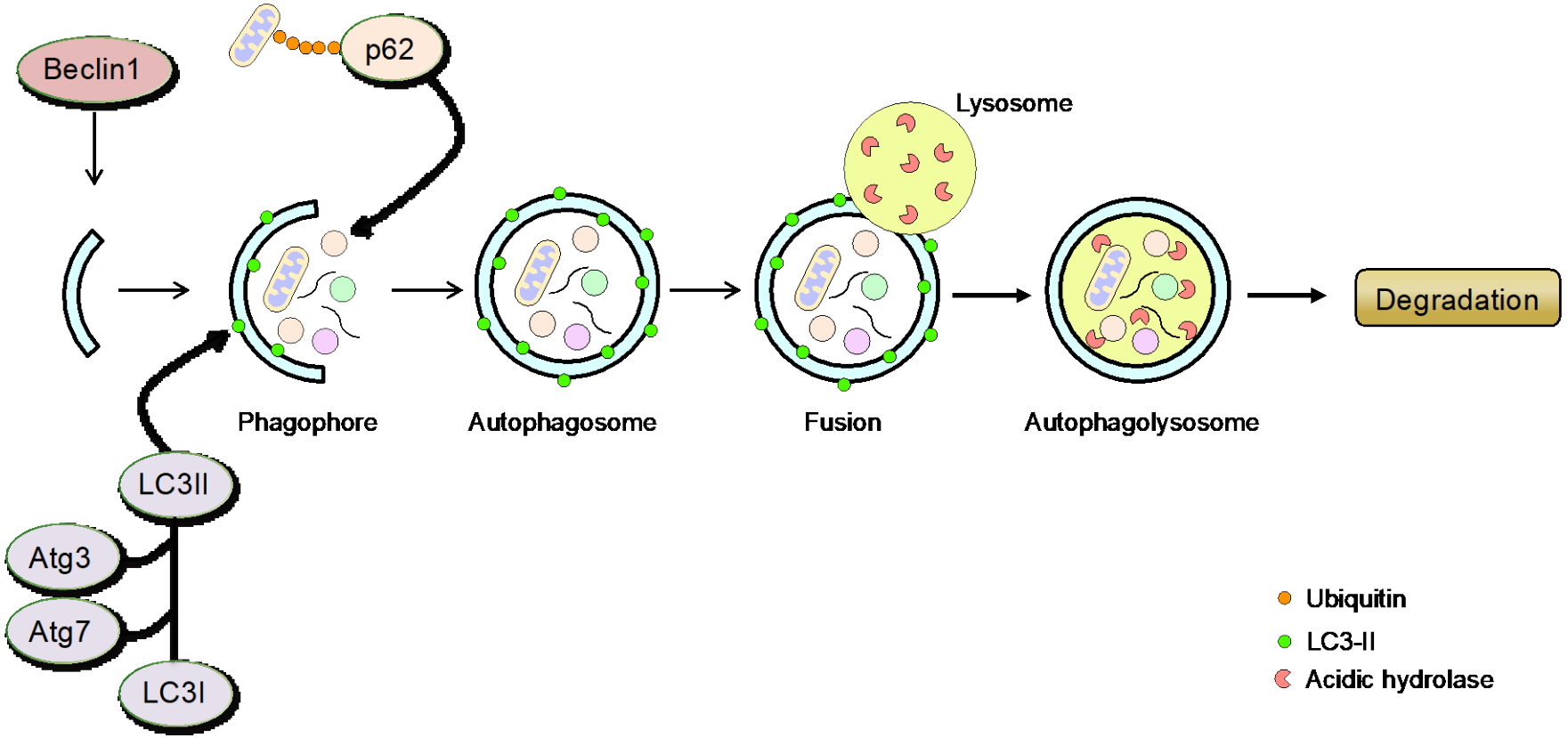
3 Objectives

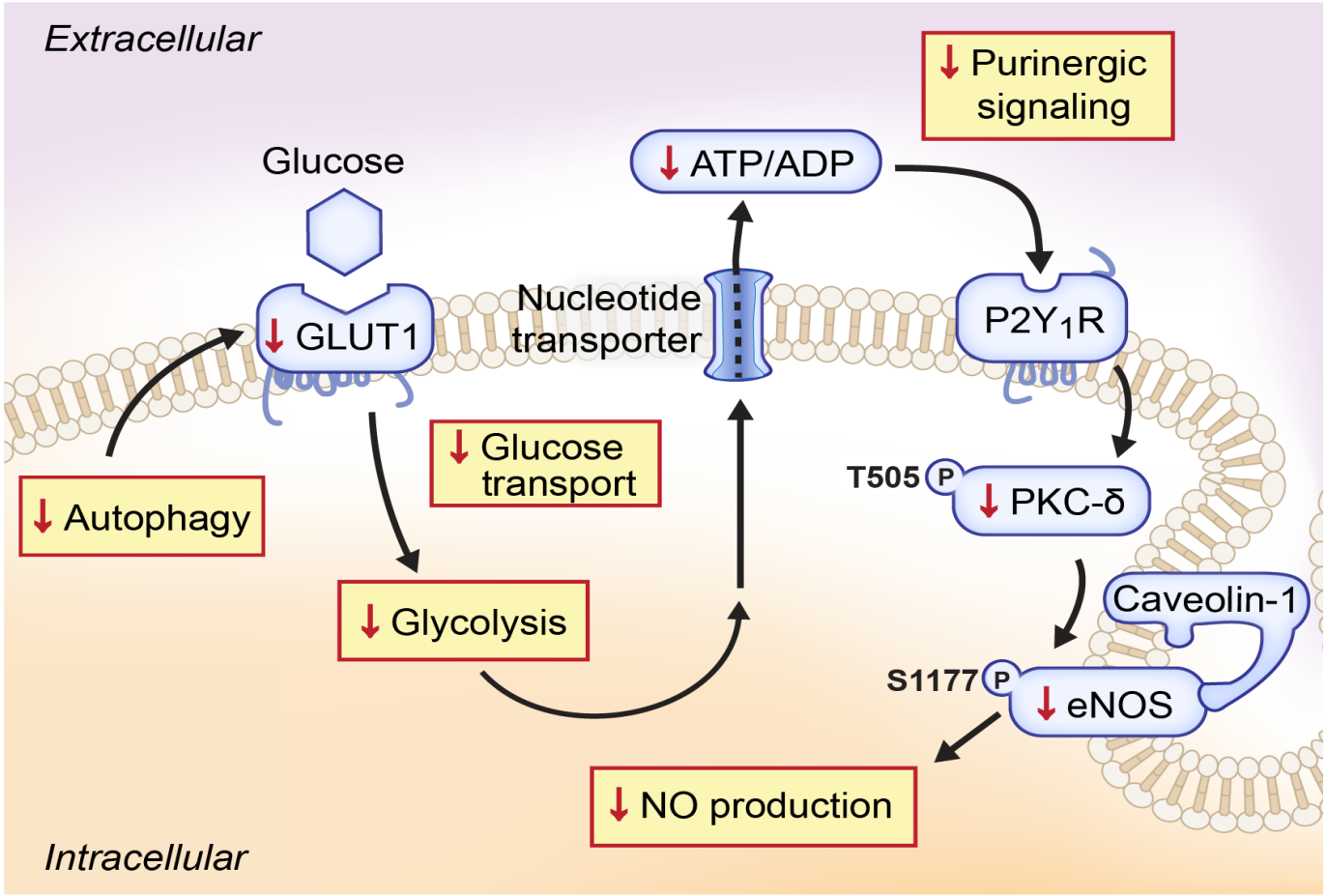
- familiarize everyone with your research interests in the area of cognitive resilience

- identifying areas for collaborations

- identifying how your research would benefit from proposed Pepper Center Core support

Autophagy





Bharath et al., *ATVB*, 2017; Park et al., *AJP-Heart*, 2019; Cho et al., *Aging Cell*, 2021; Cho et al., *Cardiovasc Res*, 2022

Functional relevance :

- Intraluminal flow-mediated vasodilation is impaired in arteries from *Atg3$^{EC-/-}$ mice*
  (Cho et al., Cardiovascular Research, 2022)

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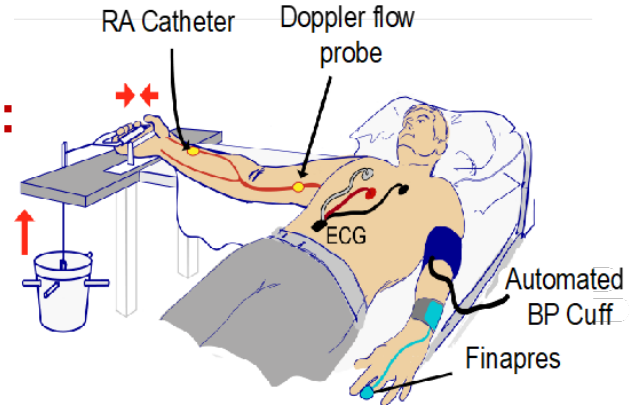
Translational relevance :



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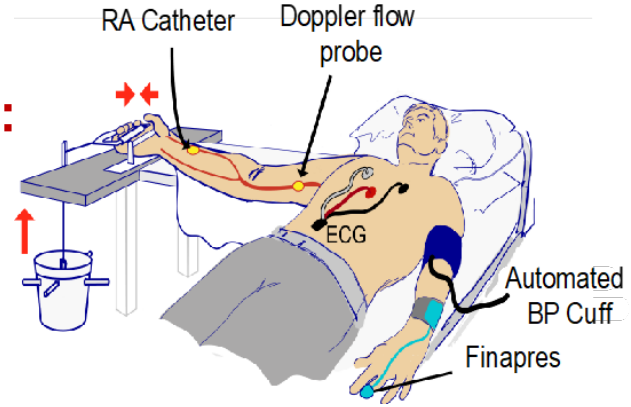
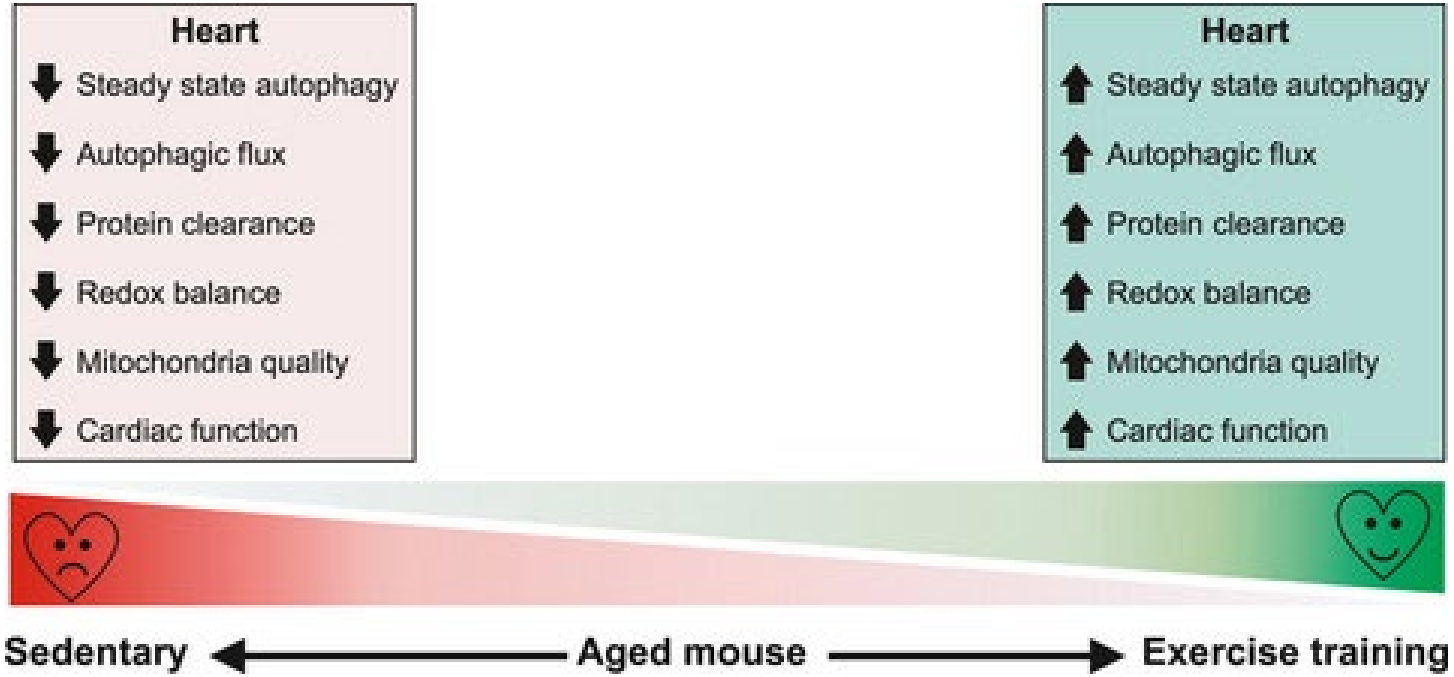


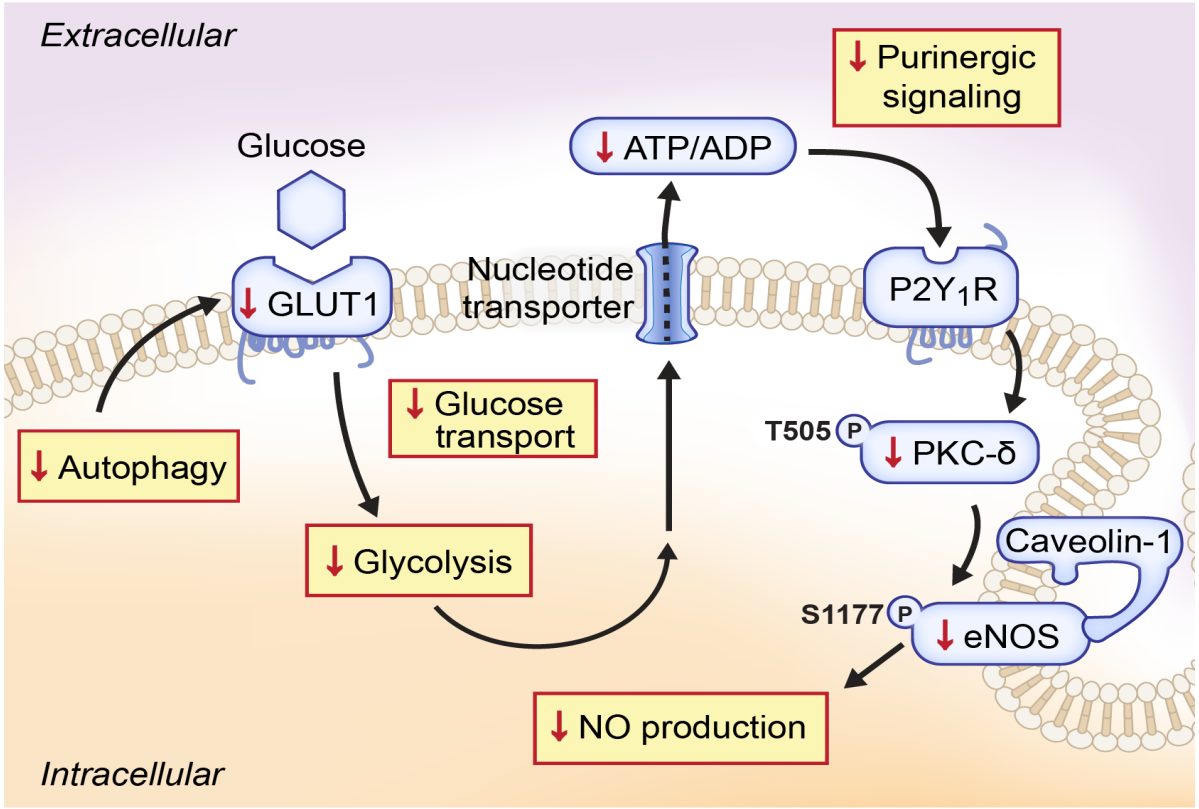
- Shear-stress evoked by functional hyperemia increases NO generation and autophagy in ECs from adult <u>but not</u> older male subjects
  *(*Park et al., *AJP-Heart,* 2019; Cho et al., *Cardiovascular Research,* 2022*)*

Autophagic flux is important in cardiomyocytes too



Cho et al, *Aging Cell,* 2021

What about the cerebral circulation ?



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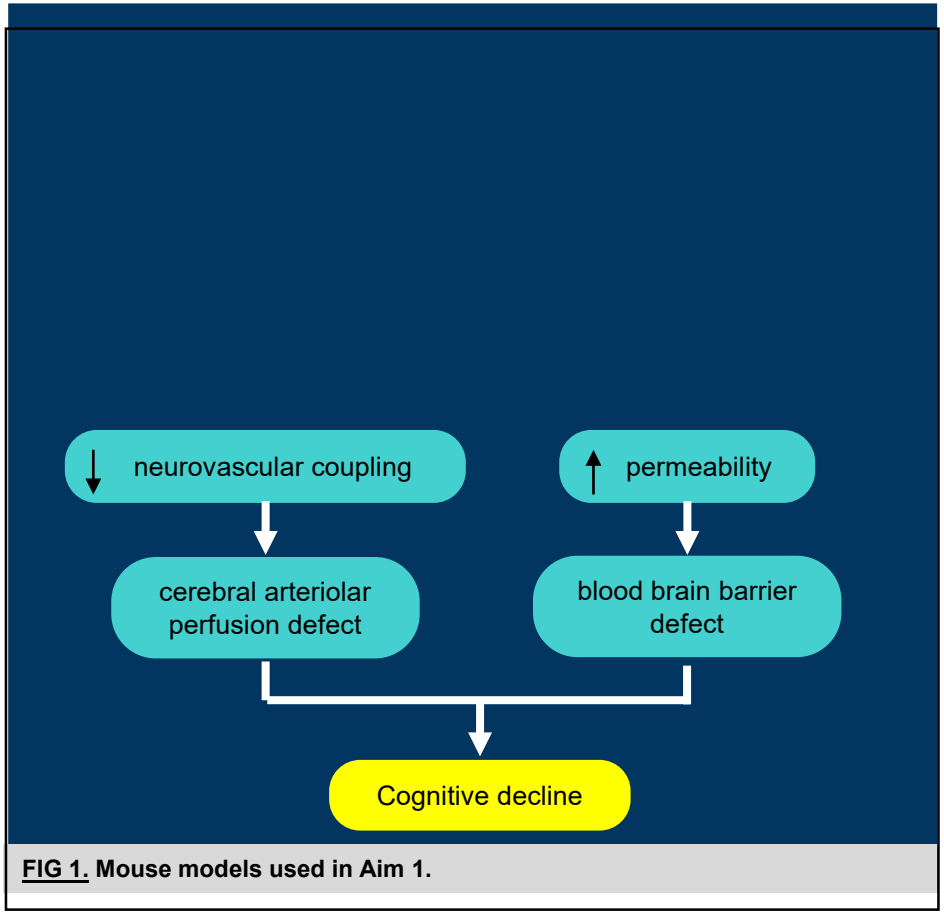
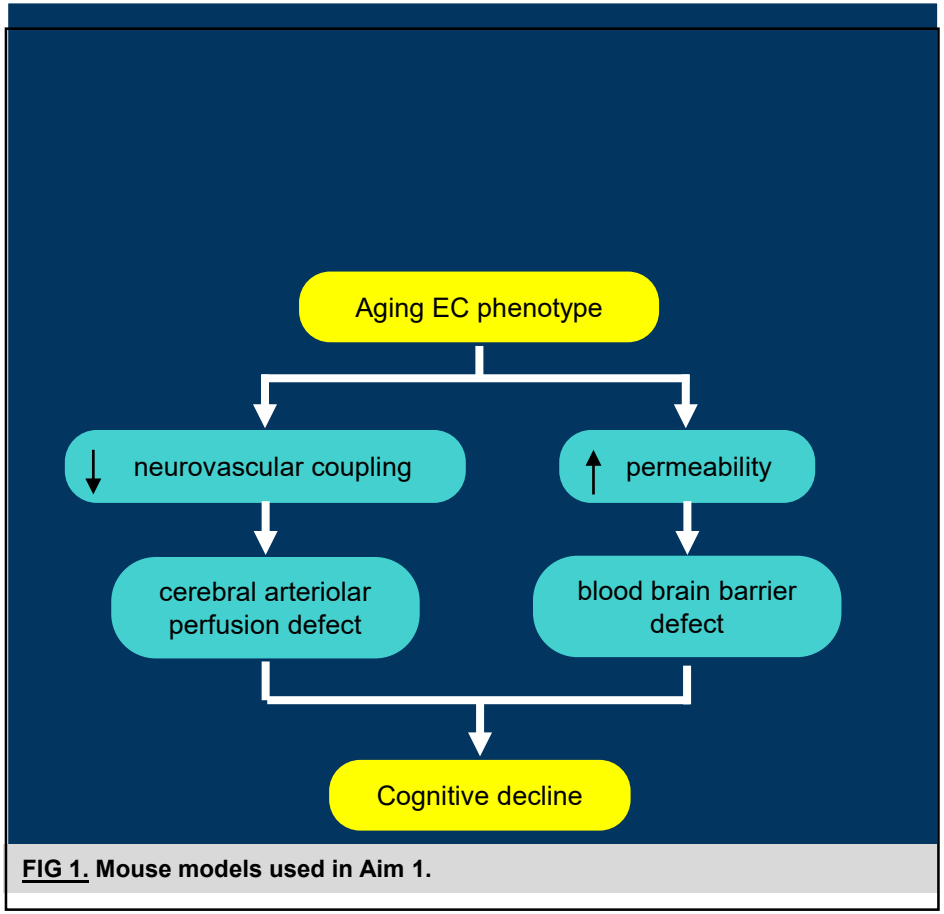


FIG 1. Mouse models used in Aim 1.



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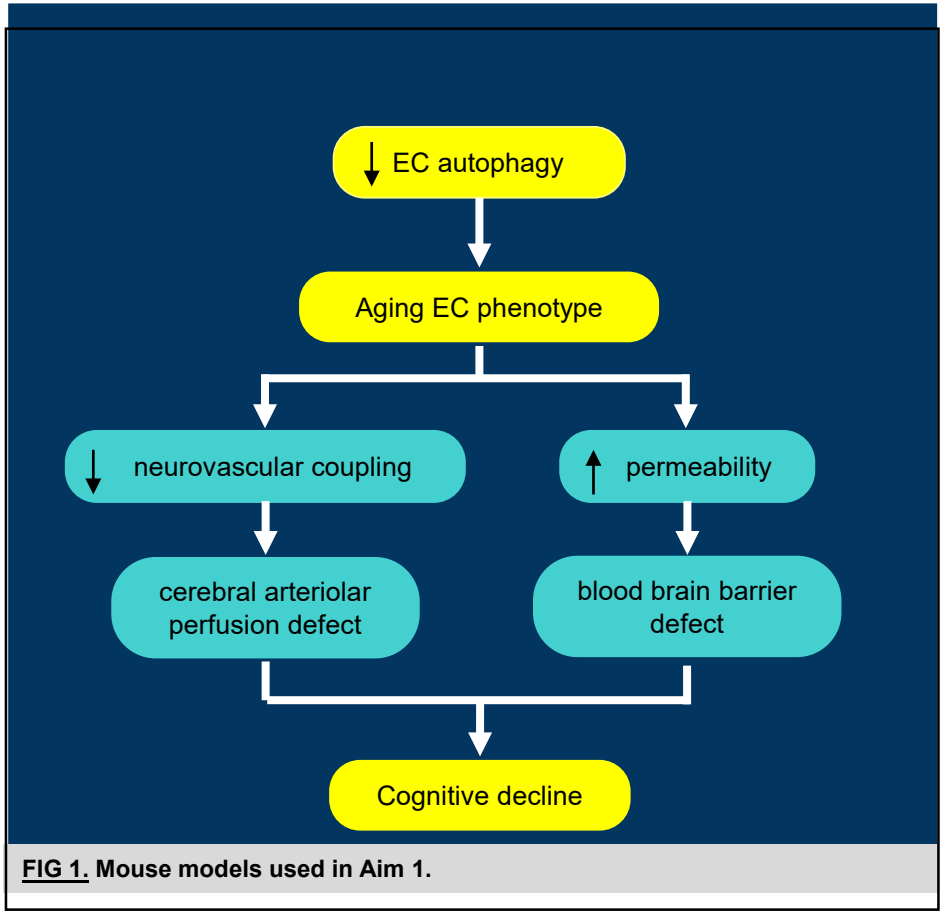

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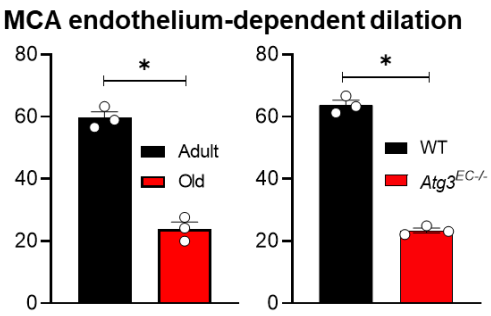

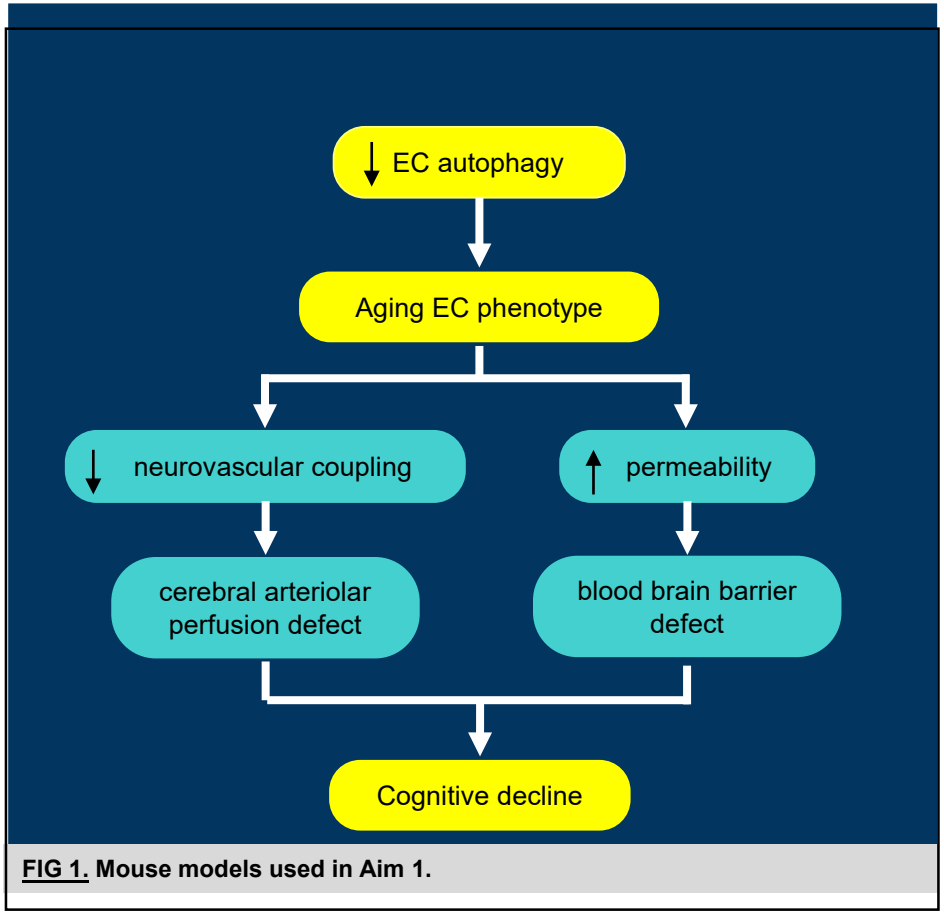

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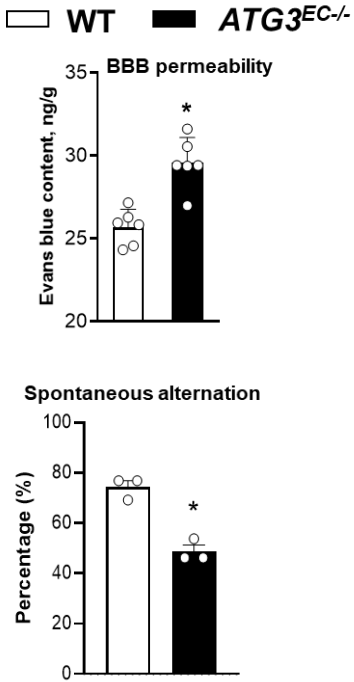
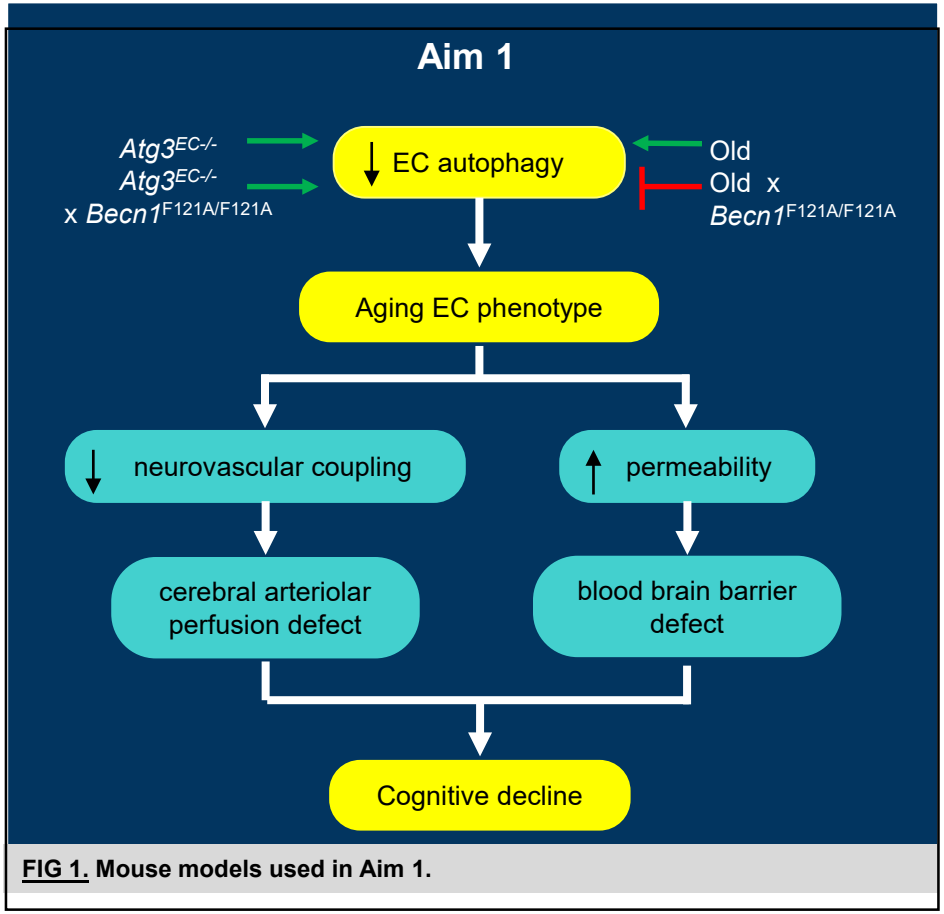


The interplay among endothelial cell (EC) autophagy, EC metabolism, and cerebrovascular resilience in the context of aging.

RO1 renewal submitted April 2022

Symons
Holland
Pires
Trinity
Rutter



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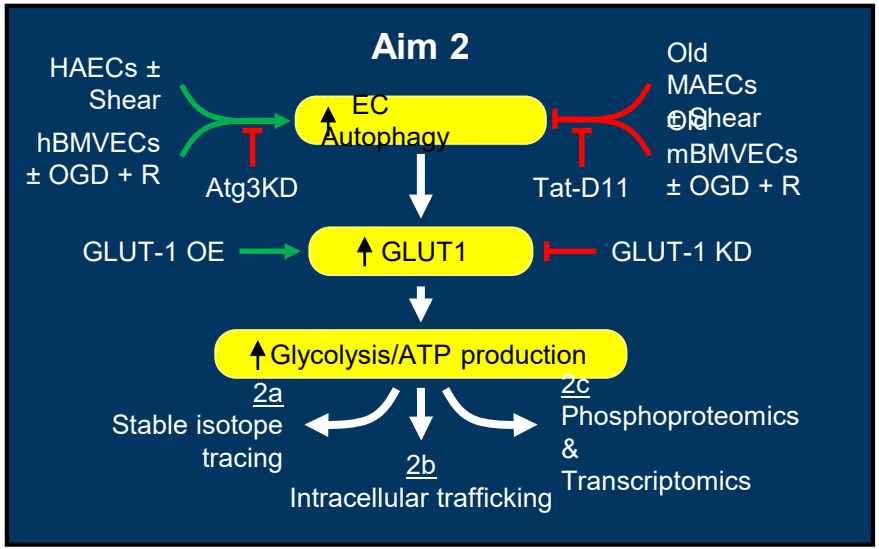
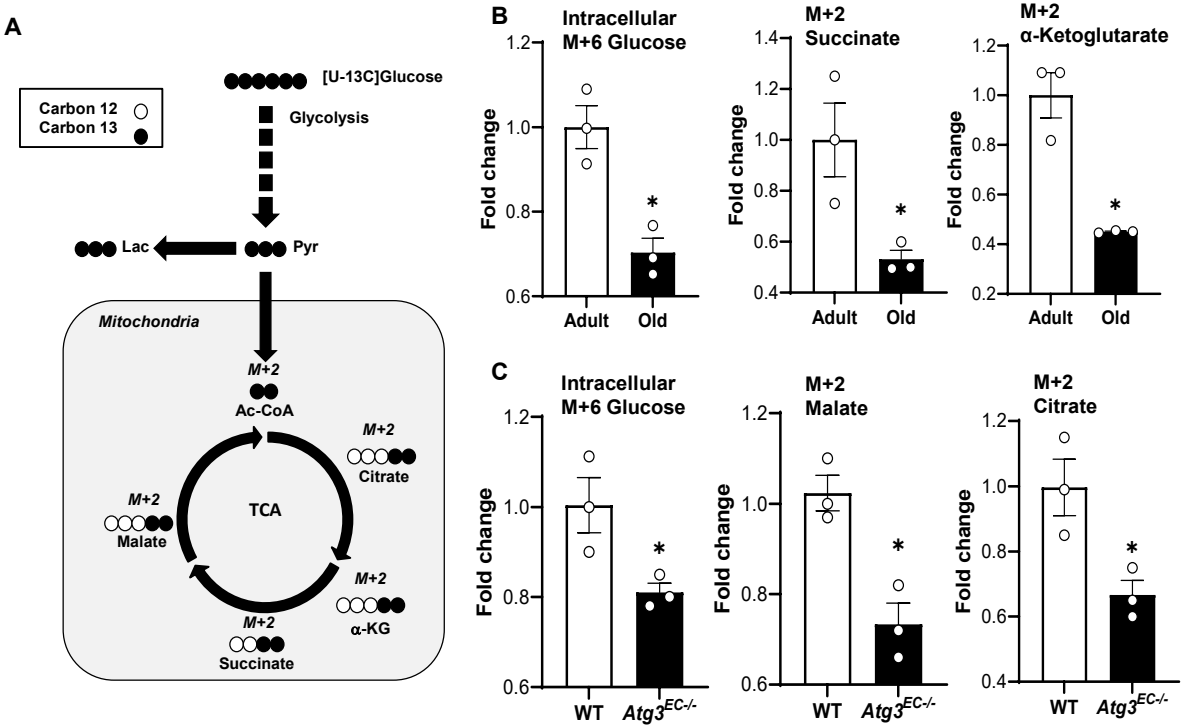
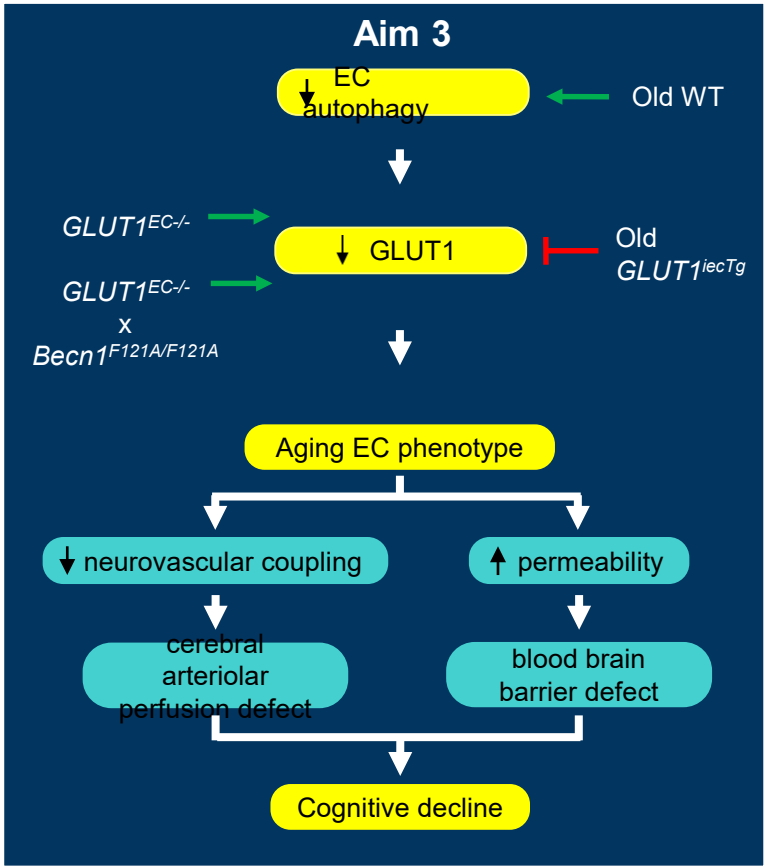

Aim 2
HAECs ± Shear
hBMVECs ± OGD + R
Atg3KD
EC Autophagy
Old MAECs ± Shear
Old mBMVECs ± OGD + R
Tat-D11
GLUT-1 OE
GLUT1
GLUT-1 KD
Glycolysis/ATP production
2a
Stable isotope tracing
2b
Intracellular trafficking
2c
Phosphoproteomics & Transcriptomics



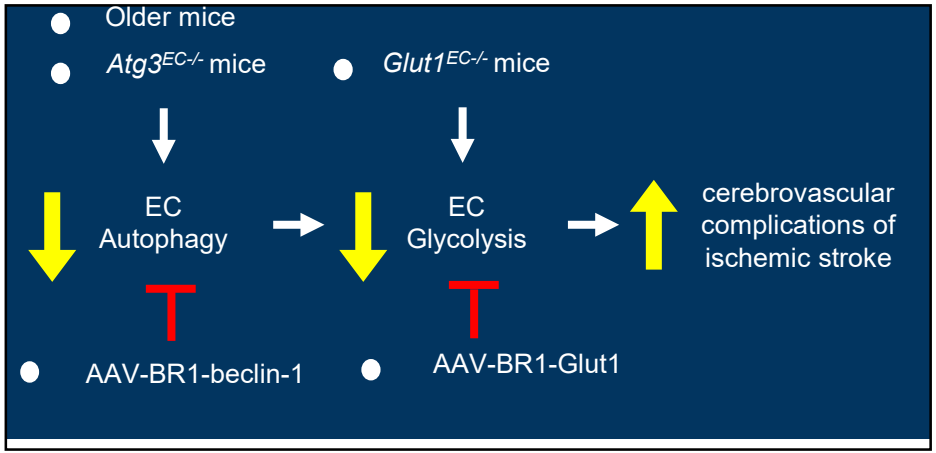
Ahmad Clunton, 2022


Aim 3
EC autophagy
Old WT
GLUT1EC-/-
GLUT1
Old GLUT1iecTg
GLUT1EC-/- x Becn1F121A/F121A
Aging EC phenotype
neurovascular coupling
permeability
cerebral arteriolar perfusion defect
blood brain barrier defect
Cognitive decline

Targeting endothelial cell metabolism to improve recovery from acute ischemic stroke in older mice

R21 planned for June 16 submission

Symons
Campbell
Denorme
Pires



3 Objectives

- familiarize everyone with your research interests in the area of cognitive resilience

- identifying areas for collaborations

- identifying how your research would benefit from proposed Pepper Center Core support

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1) Clinical Core: a well-characterized cohort of individuals interested in research participation and followed longitudinally. Building on the CoA's existing Research Participant Registry, plans for its expansion in the coming year include:

a) merging with the "Cognitive Health in Aging Database" that has its origins in the Center for Alzheimer's Research and Imaging Center,

b) incorporating the phenotypic characterization of cognitive and functional status in selected participants with an intentional plan to obtain this information in a longitudinal manner,

c) explore biorepository options to add to the cognitive and functional data,

2) Data and Biomarker Core: data management, advice about study design and analysis, biomarkers, DNA banking, and imaging,

The University of Utah
Utah Vascular Research Laboratory

Peripheral and Cerebral Vascular Function in Aging and Mild Cognitive Impairment

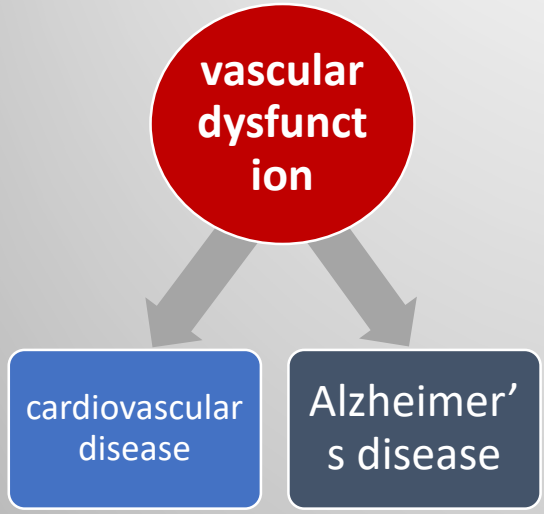
Katherine Shields

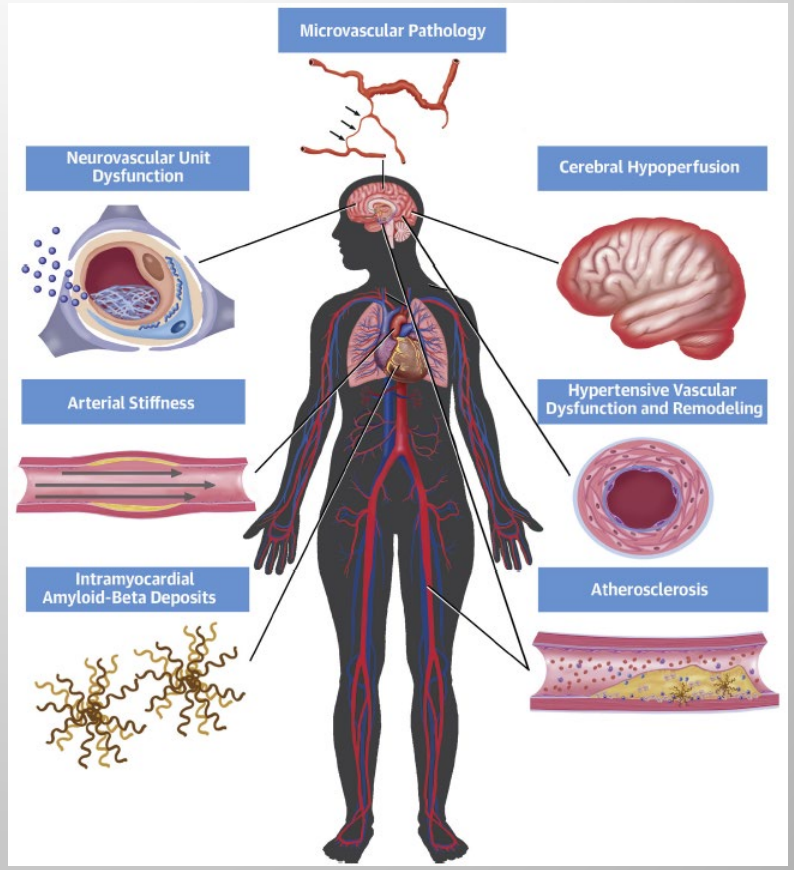
PhD Candidate, Utah Vascular Research Lab, University of Utah

Salt Lake City Geriatric Research, Education, and Clinical Center

The University of Utah
Utah Vascular Research Laboratory

Link between Peripheral and Cerebral Vasculature



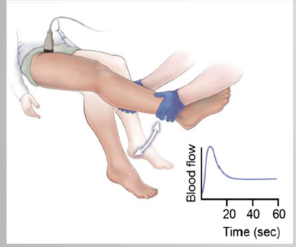


Cortes-Canteli et al, 2020

The University of Utah
Utah Vascular Research Laboratory

Vascular Function in Mild Cognitive Impairment

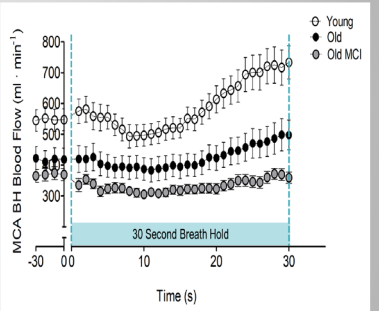
Passive Leg Movement



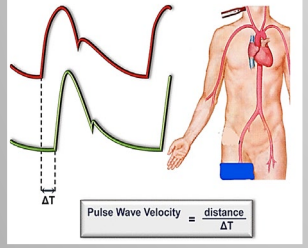
Peripheral Vasculature

Cerebral Vasculature

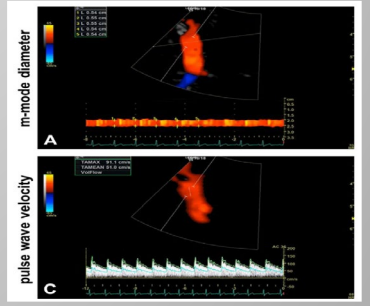
Cerebrovascular Reactivity



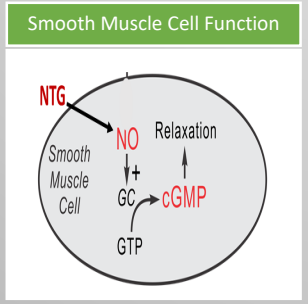
Pulse Wave Velocity



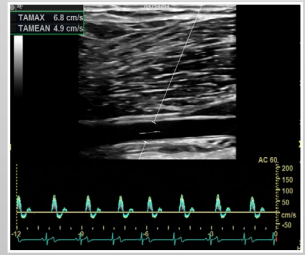
Middle Cerebral Artery Blood Flow



Smooth Muscle Cell Function



Resting Blood Flow

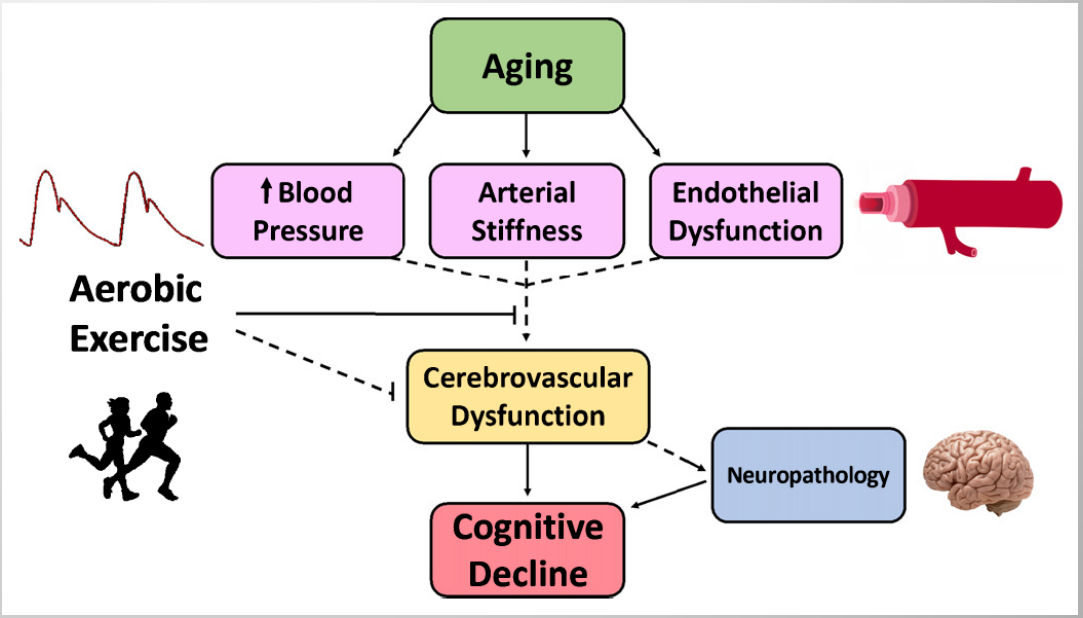


Venous Blood Draw

The University of Utah
Utah Vascular Research Laboratory

Future Research & Collaborations

- Healthy aging, MCI, & Alzheimer's Disease
- Long term follow-up
- Additional vascular function assessments
- Alzheimer's disease specific tests
- Exercise interventions
- Participant recruitment



Barnes et al, 2018

EEG Applications in Cognitive Resilience

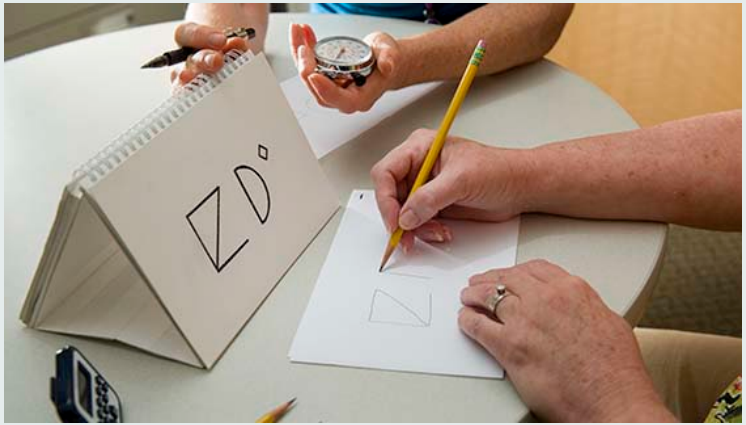
General and disorder-specific risk markers

Matt Euler, PhD

matt.euler@psych.utah.edu

Neuropsychology and Neural Dynamics Lab

Interdisciplinary Focus: EEG applications to clinical neuropsychology



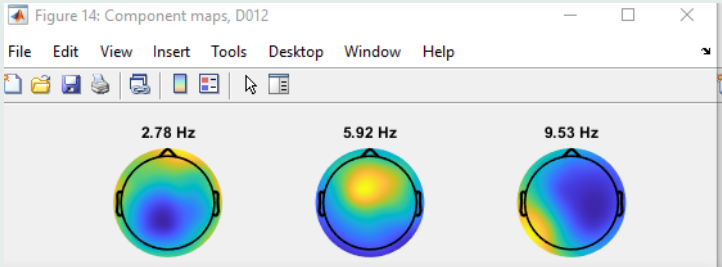
Research Interests

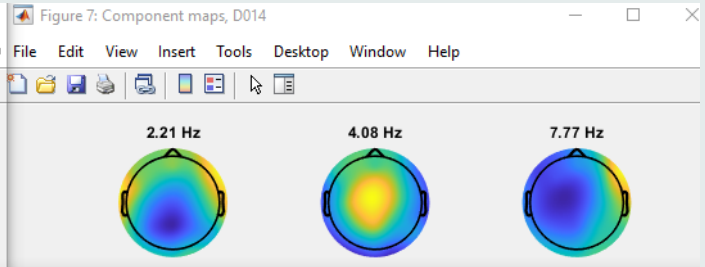
- **Current studies are examining:**
  - EEG markers of Alzheimer's disease risk
  - Risk for lapses in cognitively-healthy older adults

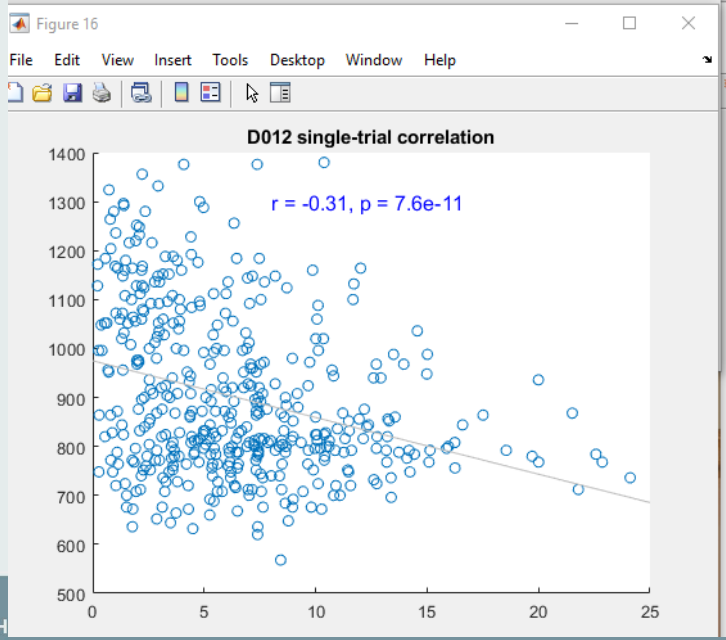
- **Long-term goal**
  - Develop EEG "stress tests" for cognition
  - Reliable and valid markers that predict age-associated cognitive disorders *and* cognitive risk in healthy aging
  - Assess translational potential and feasibility

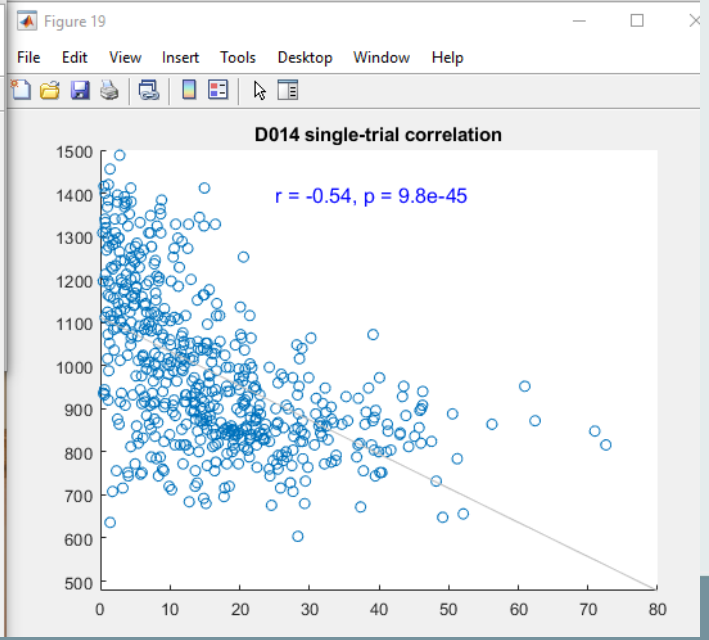
Current Grant:

- Low-frequency power correlated to reaction time
- Healthy older adults shown
- Will extend to MCI and AD







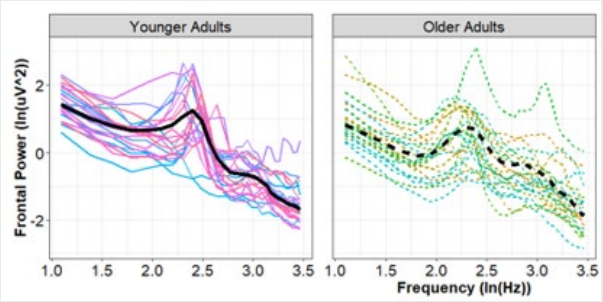


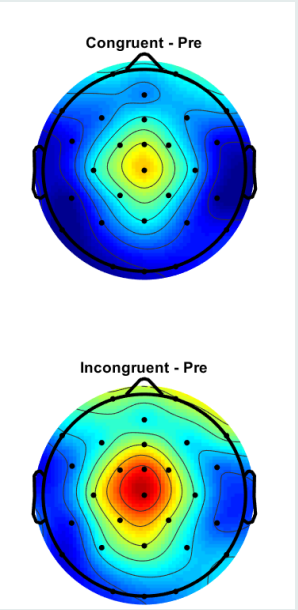
Areas for Collaboration

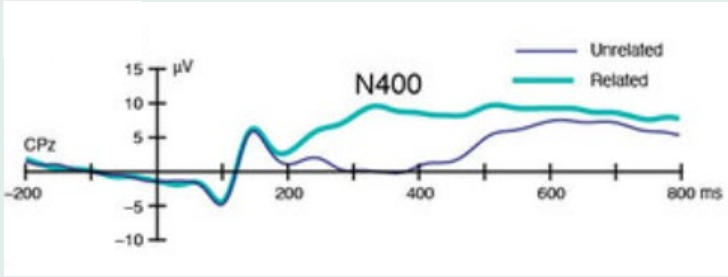
- **EEG, individual differences, cognitive functioning and performance**
  - Neuropsychological assessment
  - Experimental task development
  - EEG signal processing

Areas for Collaboration

- **EEG Markers**:
  - Resting and task-related
  - ERP, frequency- and time-frequency analysis
  - Oscillatory/aperiodic activity
  - Intra-, inter-individual variability, connectivity, others…

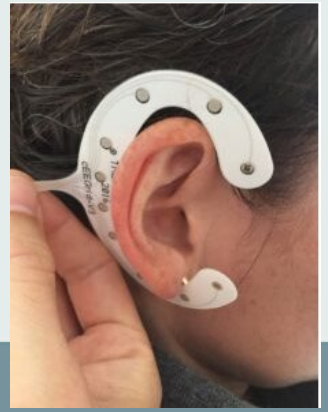






Potential Areas for Pepper Center Support

- **Core support: Clinical and Biomarker Cores**
  - Recruitment assistance
  - Opportunities to correlate EEG variables with cognitive assessments
  - Access to other biomarkers: neuroimaging, fluid biomarkers, etc.
  - Incorporating EEG into baseline assessments of longitudinal cohorts?



Thanks!

- matt.euler@psych.utah.edu
- @meuler_

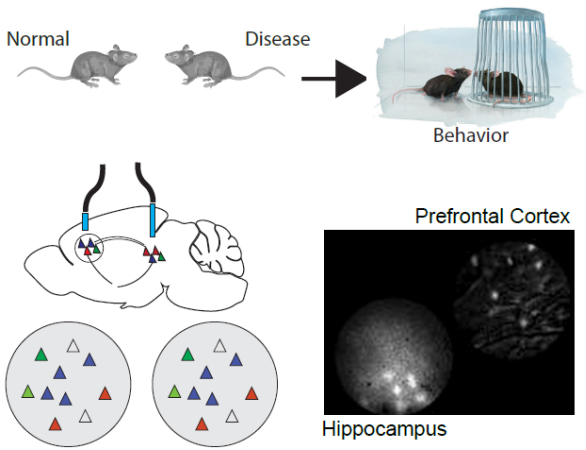
Distributed Networks Underlying Cognition in Neurodegenerative Disease

Nick Frost MD, PhD
University of Utah
Department of Neurology

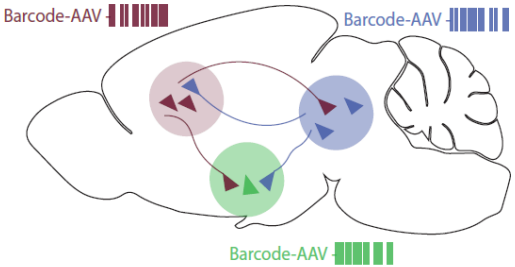
Agenda

1. About Me
    a. Started independent laboratory at U of Utah July, 2021
        a. Continuing work focused on network activity in ASD
        b. Currently building projects focused on understanding how cortical microcircuit activity changes in neurodegeneration
    b. I see patients in cognitive neurology

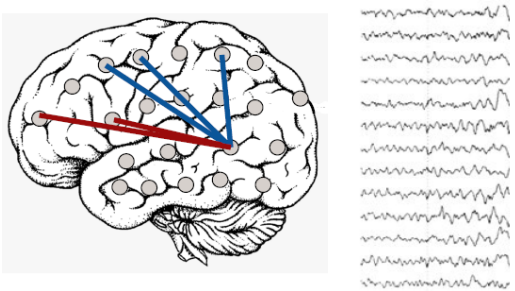
2. 5-minute blitz overview of the laboratory
    a. Microcircuit computations underlying information routing in neurodegenerative disorders
    ~~b. Distributed brain states in healthy aging and AD via EEG~~



How is neuronal activity organized across distributed circuits in the healthy and diseased brain?



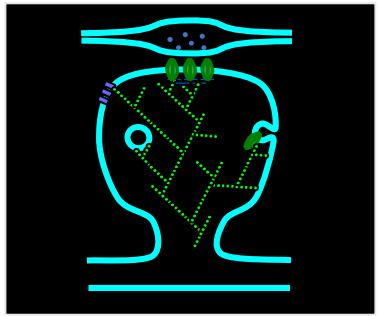
How does disease alter the anatomical connections between brain regions at the cellular level?



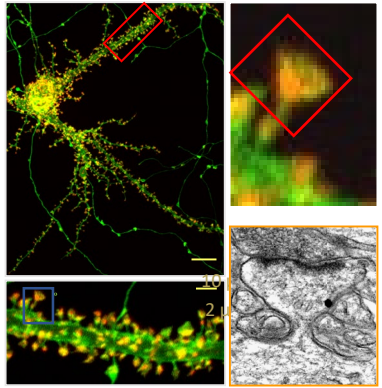
How does disease alter the computations necessary for communication within the brain?

The brain functions across multiple scales

Molecular

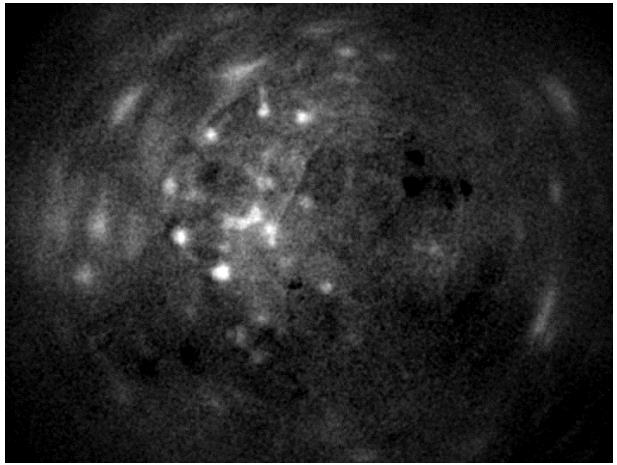


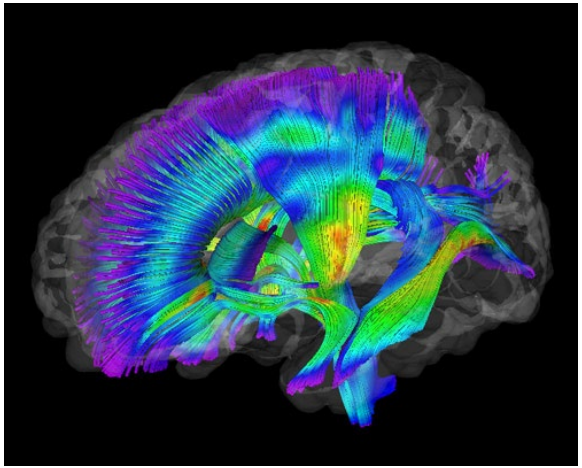
Cellular



Synaptic

Local and Distributed Networks



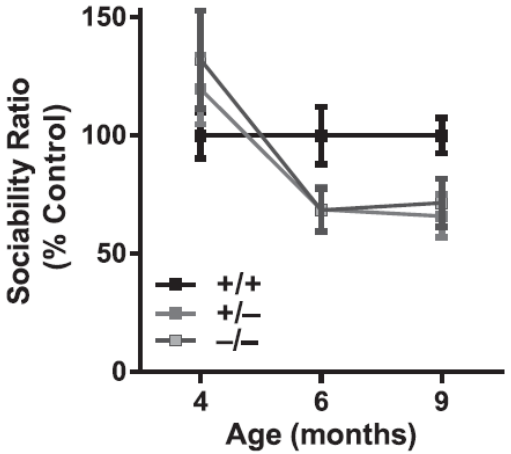


Principles of social interaction are conserved across species

- Depend on activity in the prefrontal cortex and its connections
- Impairments in social interaction seen in patients with neurodevelopmental disorders as well as neurodegeneration
- Understanding circuit-level dysfunction will be critical to restoring normal behavior
- Social interaction is protective against incipient neurodegeneration (Wilson et Bennett, 2007; Amieva, 2010; Hsiao, 2018)

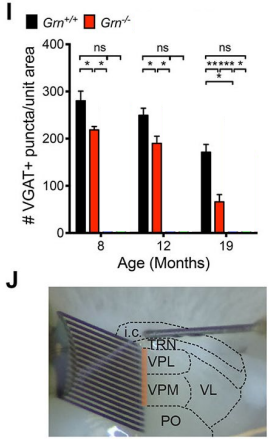
Circuit mechanisms underlying abnormal social behavior in FTD

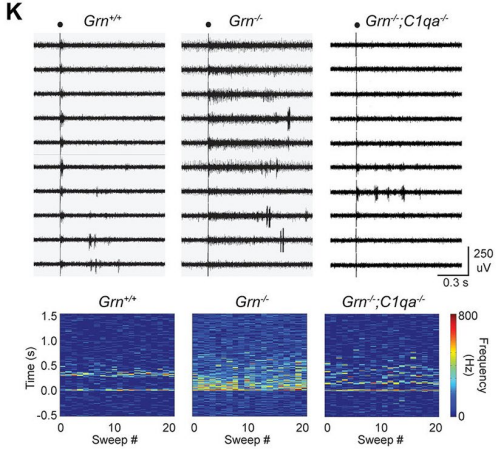
Abnormal Social interaction in progranulin-deficient mice



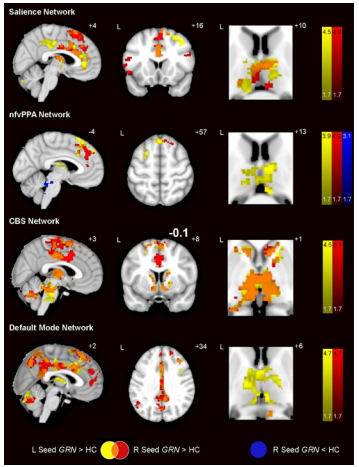
Filiano, 2013

Early loss of inhibitory synapses leads to hyperexcitable thalamocortical circuits



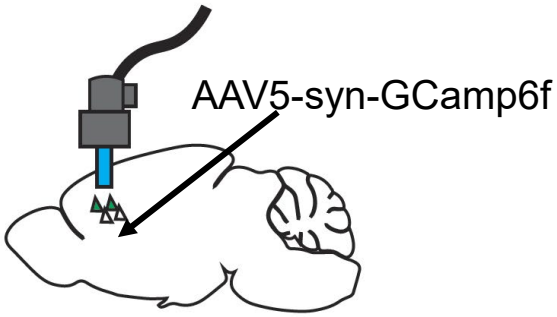


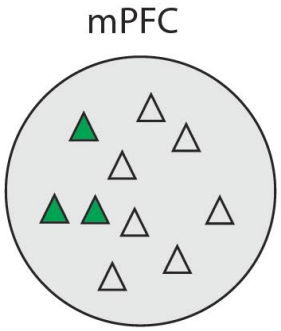
Lui et Huang, 2016

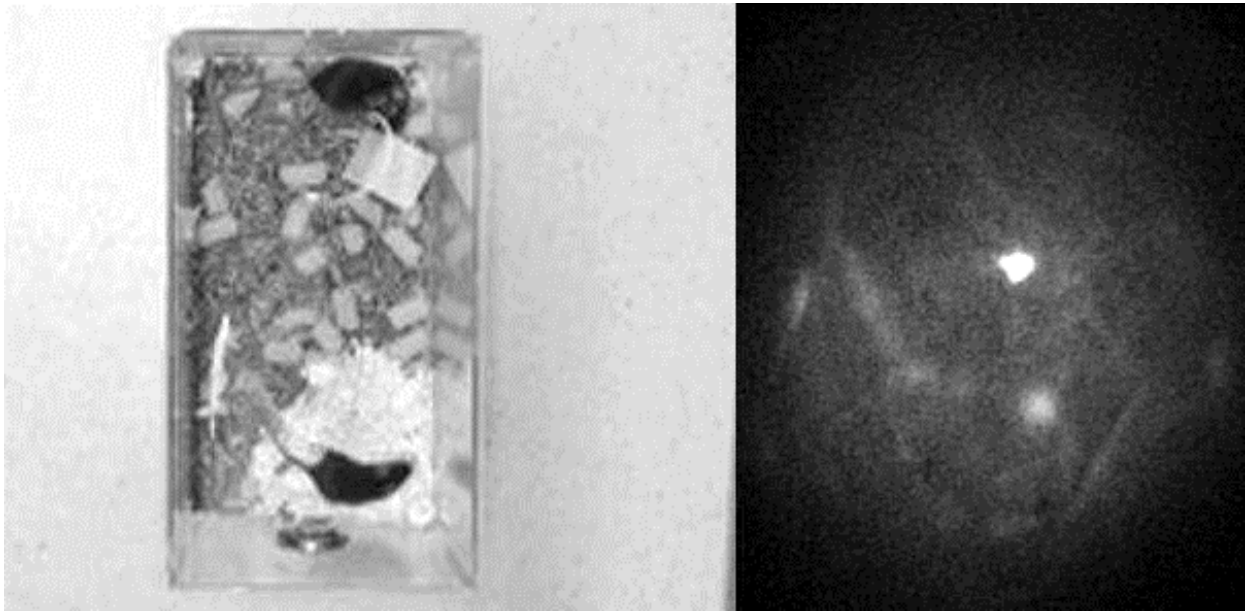


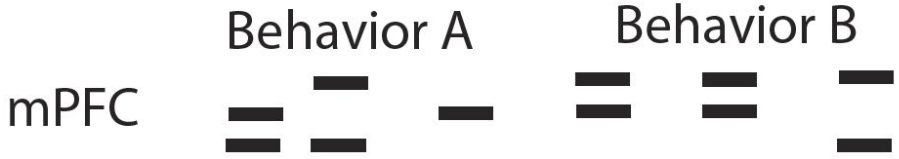
Lee et Seeley, 2019

Imaging PFC activity during social interaction

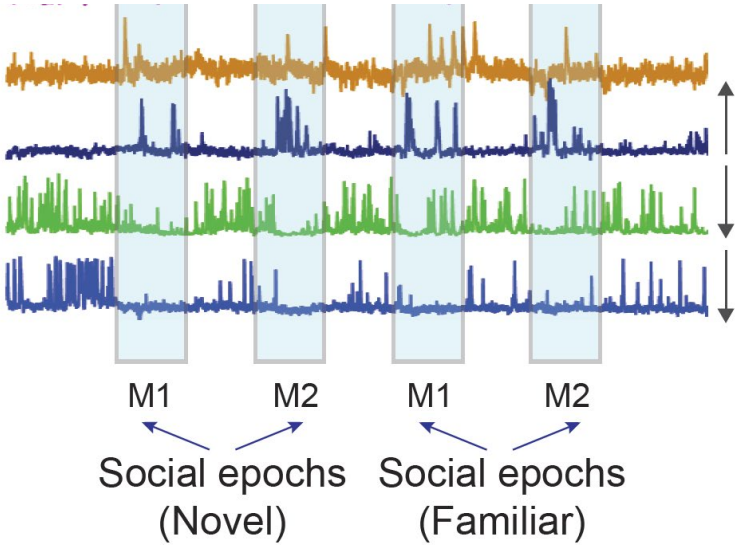


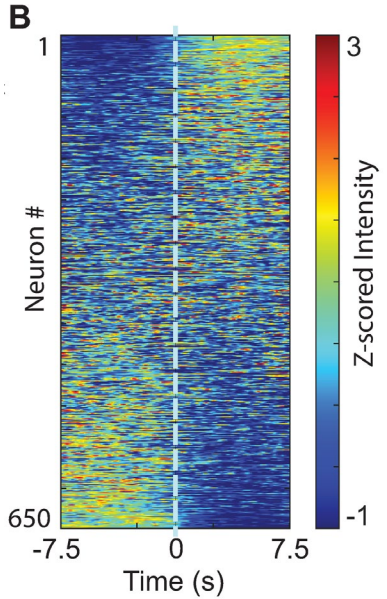


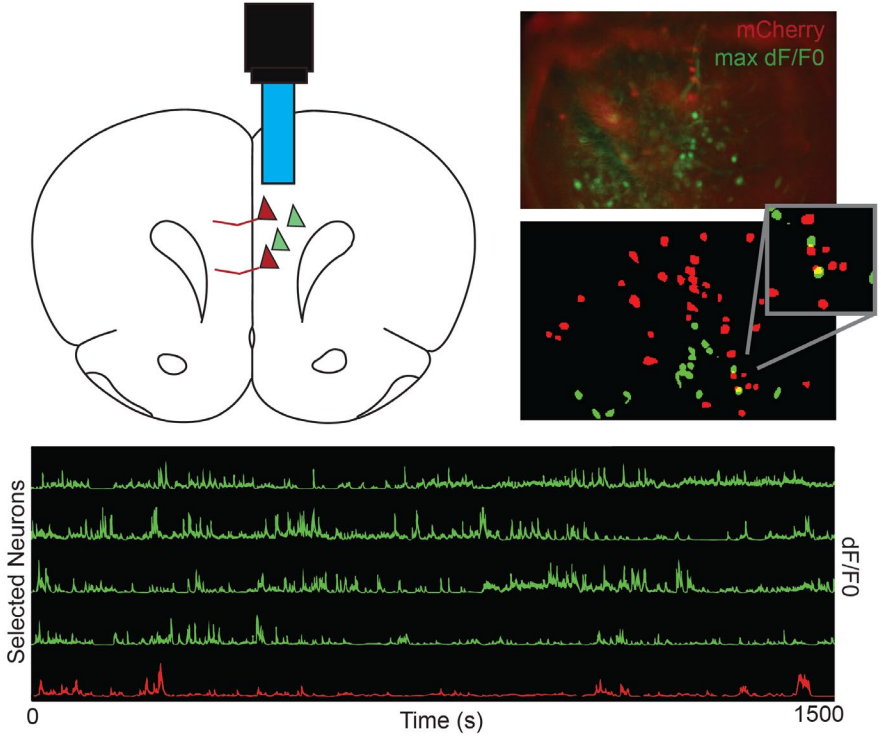




PFC activity is modulated during social interaction



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dF/F0
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Time (s)
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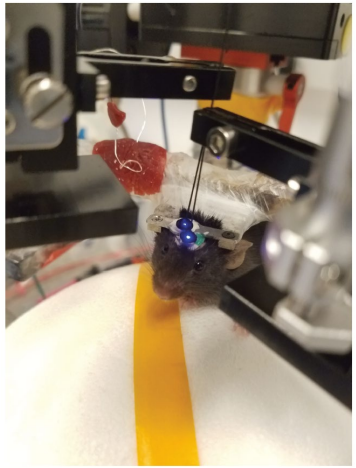
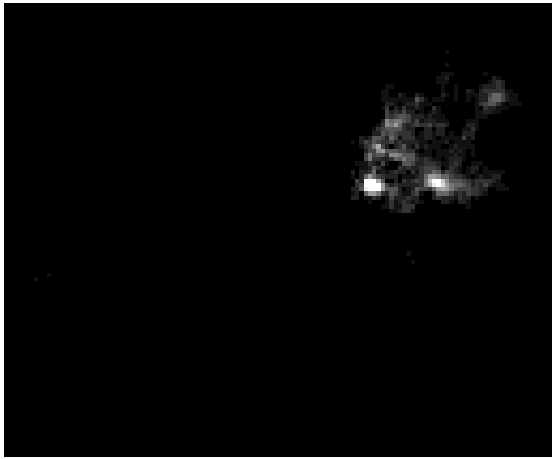
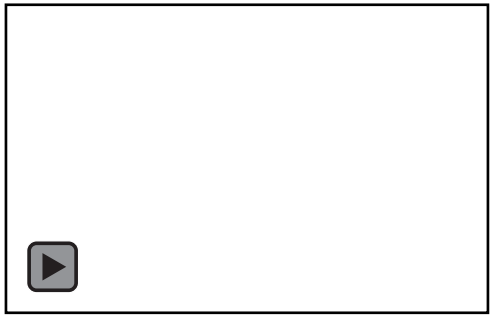
Disassembling distributed cell assemblies



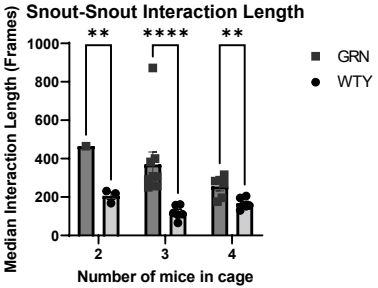


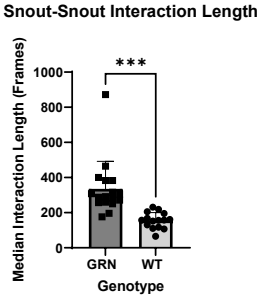
Monitoring social interaction in Grn R493X mice (5 months)

Interactions within home cage

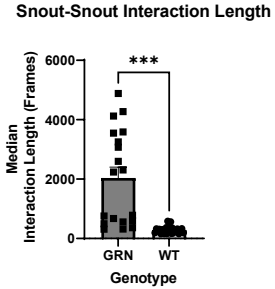


Home Cage

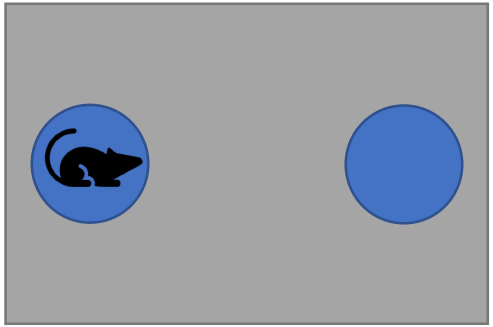


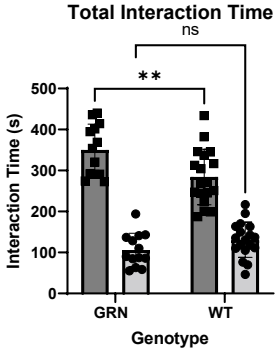


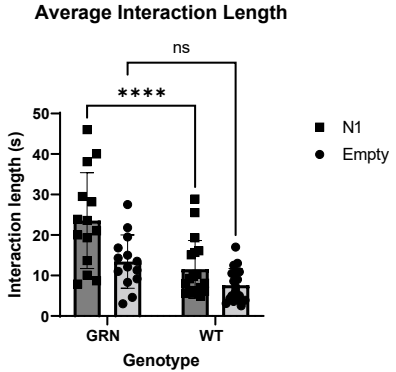
Novel Juvenile



Social Preference Test







Hailee Walker

Thank you!

Lab Members
Nathan Johnston
Hailee Walker
Marina Yang
Claire Park
David Park
Duc My Vo

Come visit us!
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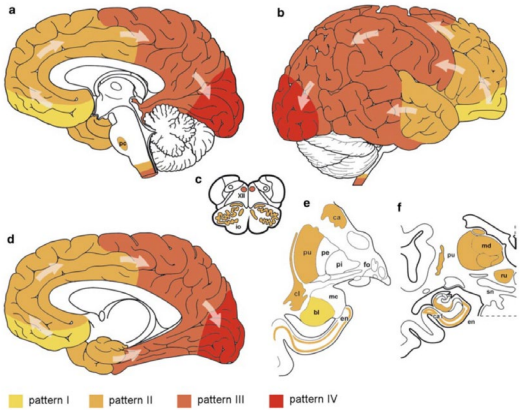
@nickfrostneuro

NIH National Institute of Neurological Disorders and Stroke
SIMONS FOUNDATION

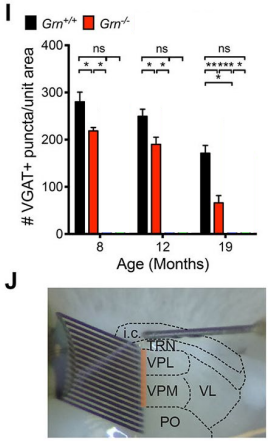
Circuit mechanisms underlying abnormal social behavior in FTD

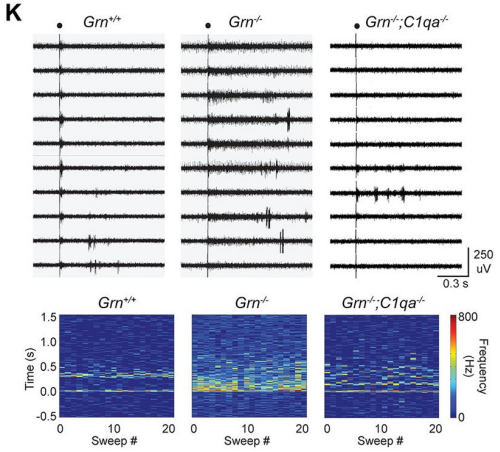
Involvement of subcortical structures in FTD

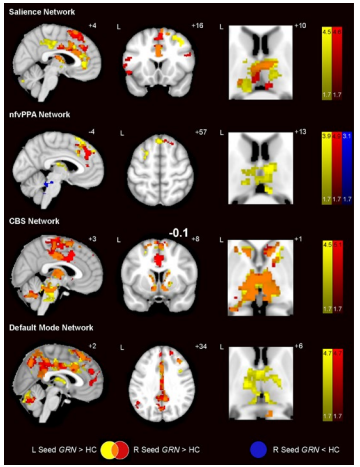


Brettschneider, 2014

Pruning of inhibitory neurons in progranulin deficiency precedes neurodegeneration and leads to hyperexcitable thalamocortical networks







Lui et Huang, 2016

Lee et Seeley, 2019

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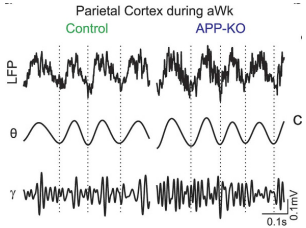
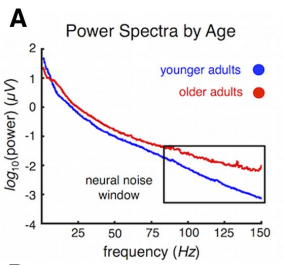
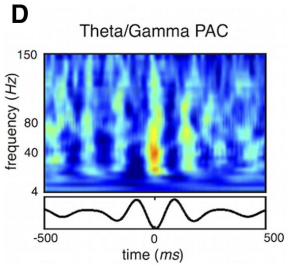
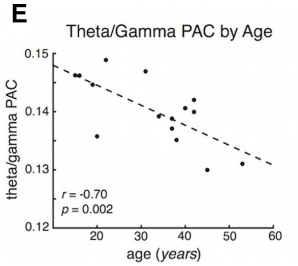
Distributed computations in normal aging and disease



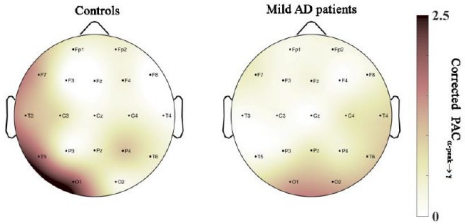
Zhang et Draguhn, 2015







Voytek et Gazzaley, 2015



Poza et Hornero, 2017

1. How does PAC across distributed circuits change in the aged or diseases brain?
2. How is PAC across distributed circuits modulated by cholinergic input?
3. Can we use PAC to predict cognitive decline?