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Scientifically Redefining ME/CFS

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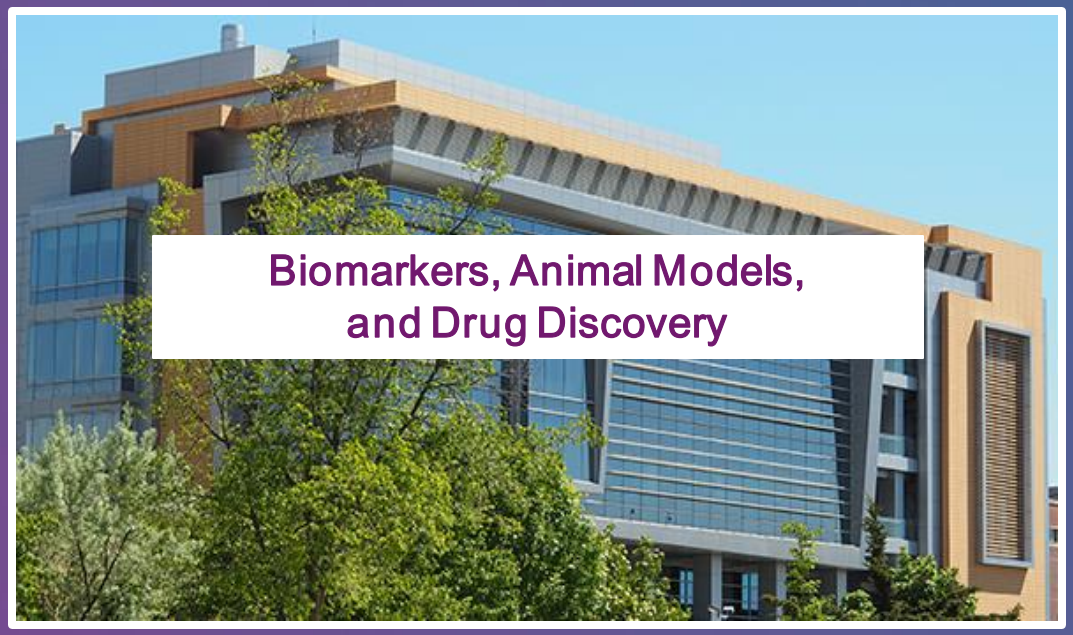
Multidisciplinary Translational Science

Sierra Internal Medicine/Simmaron Clinic

Incline Village, NV

Simmaron R&D LAB



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2023 Projects

mTOR Activation, Autophagy Impairment and ME/CFS

Animal Model Development

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2023-2025 Funding

- NIH R21 NS129021-01A1
- Solve M.E. Ramsay Award
- Parasol Tahoe Community Foundation

Cornell University Founded A.D. 1865

NIH National Institute of Neurological Disorders and Stroke

searchMECFS

Coppe Laboratories

Solve M.E.

RTI International

Milwaukee Institute for Drug Discovery
University of Wisconsin-Milwaukee

University of Wisconsin UWMilwaukee

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Dr. Avik Roy, PhD

mTOR Activation, Autophagy Impairment, and ME/CFS

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Background

- ME/CFS is a chronic multisystem disease characterized by muscle fatigue, muscle pain, and brain fog.
- Cardinal symptoms: Post-exertional malaise (PEM) and Orthostatic intolerance (OI).
- Until now, the molecular mechanism is not known.
- Potential contributing factors to the pathogenesis of ME/CFS
  - mitochondrial toxicity (Hanson et al., 2016)
  - upregulations of inflammatory cytokines (Mandarano et al., 2020),
  - Myelin abnormalities (Morris and Maes, 2013).
  - autophagy impairment (Gottschalk et al., 2022)

- Challenges
  - Lack of post-mortem samples such as brain, muscle, and spinal cord tissue.
  - Highly heterogeneous etiology of the disease.
  - Lack of a reliable animal model.

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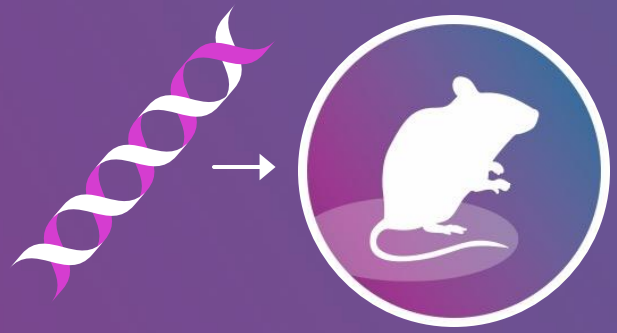
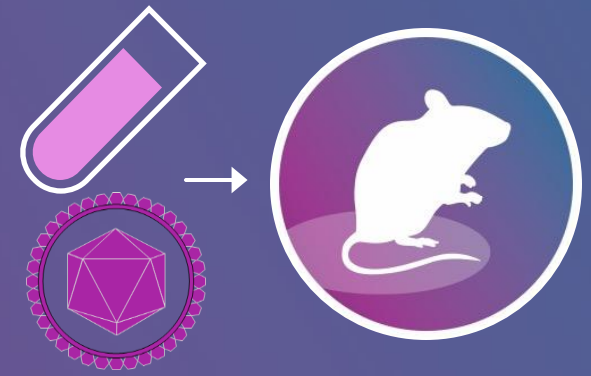
Our goal

To make a disease model that successfully displays PEM

Drug-induced mouse model



Transgenic mouse model



Disease-relevant such as virus-induced or plasma-infused mouse model

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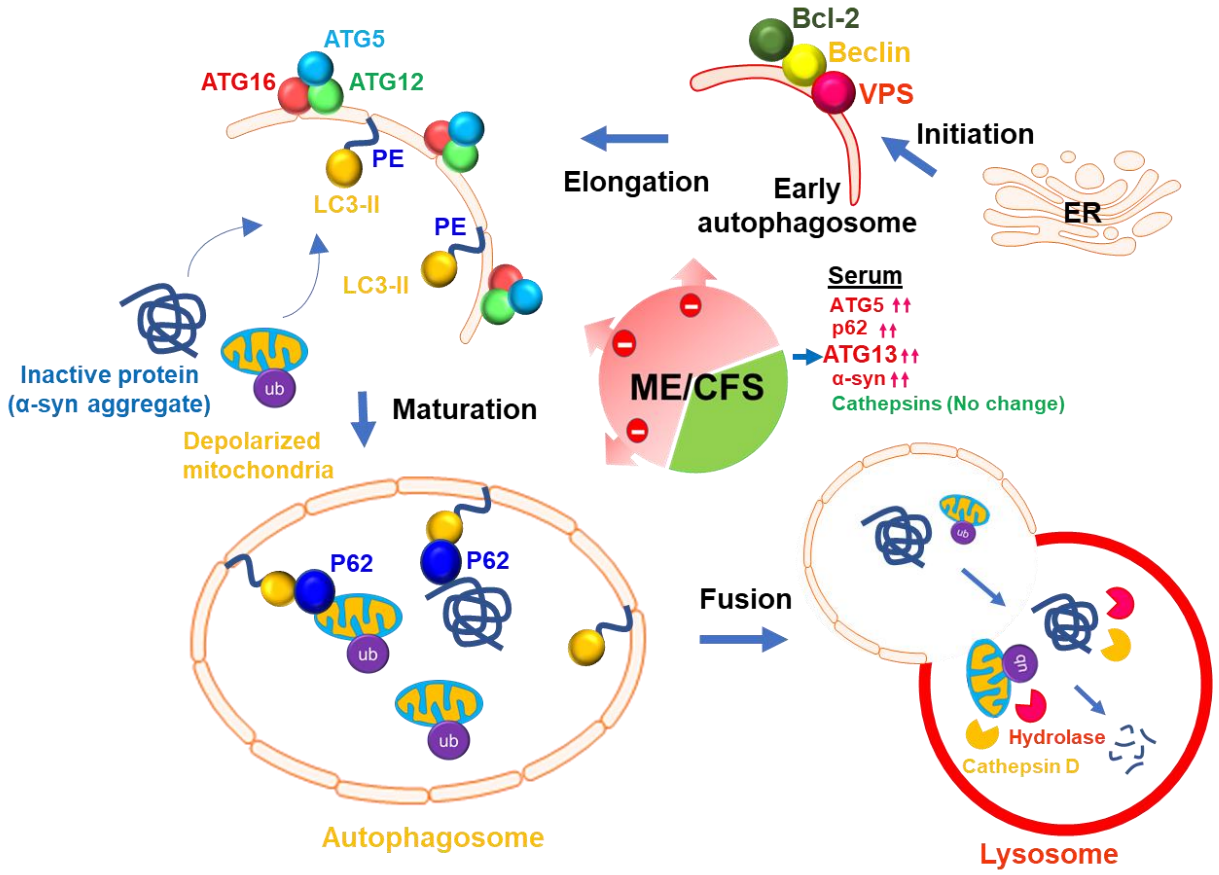
Autophagy: Targeted Pathway



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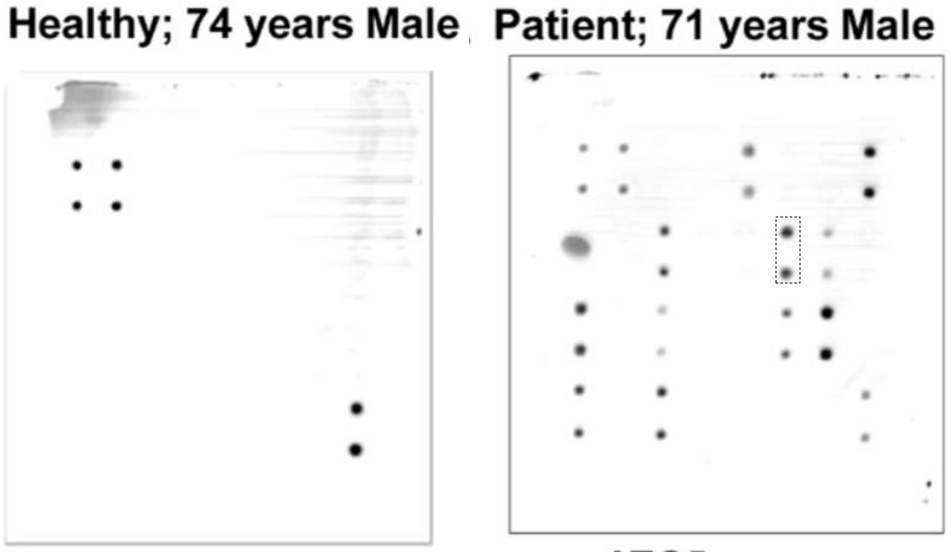
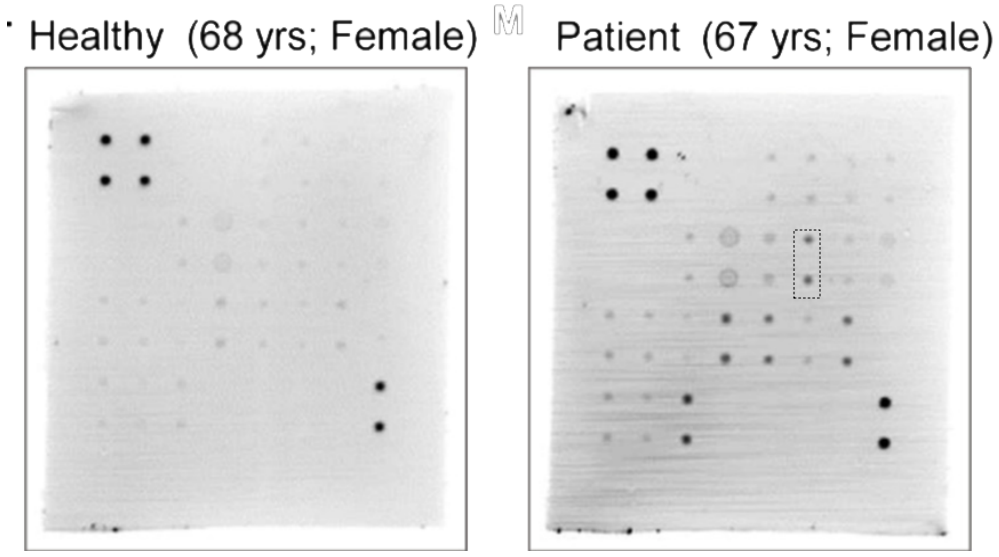
Scientific Premise

In ME/CFS patients, ATG13 inactivation leads to the autophagy impairment



Antibody array



Antibody array

 Mol Cell Neurosci 2022; *DOI: 10.1016/j.mcn.2022.103731*

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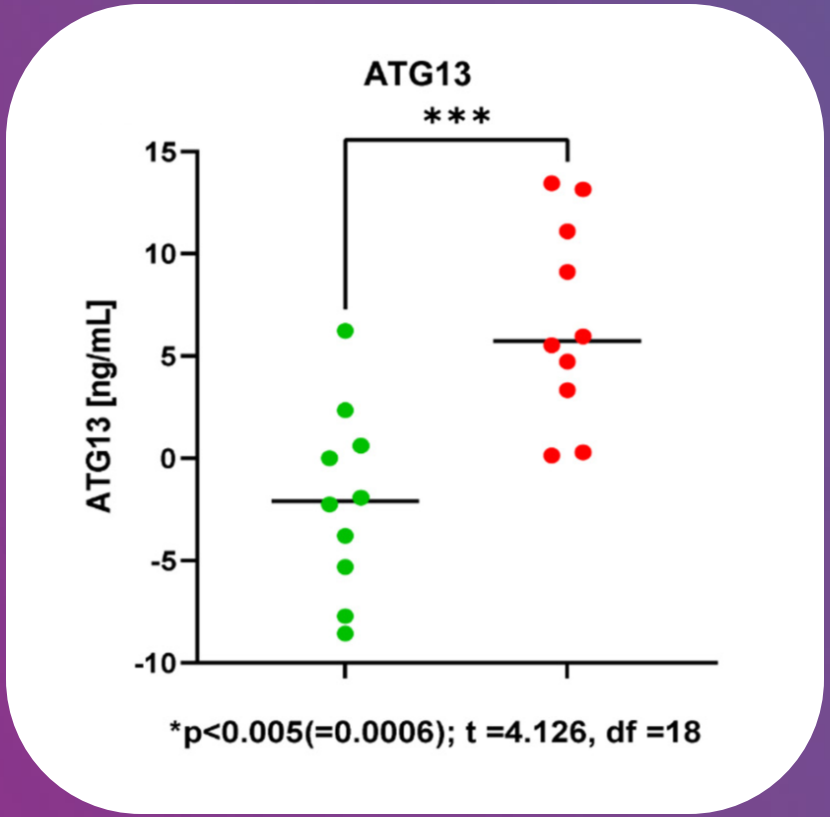
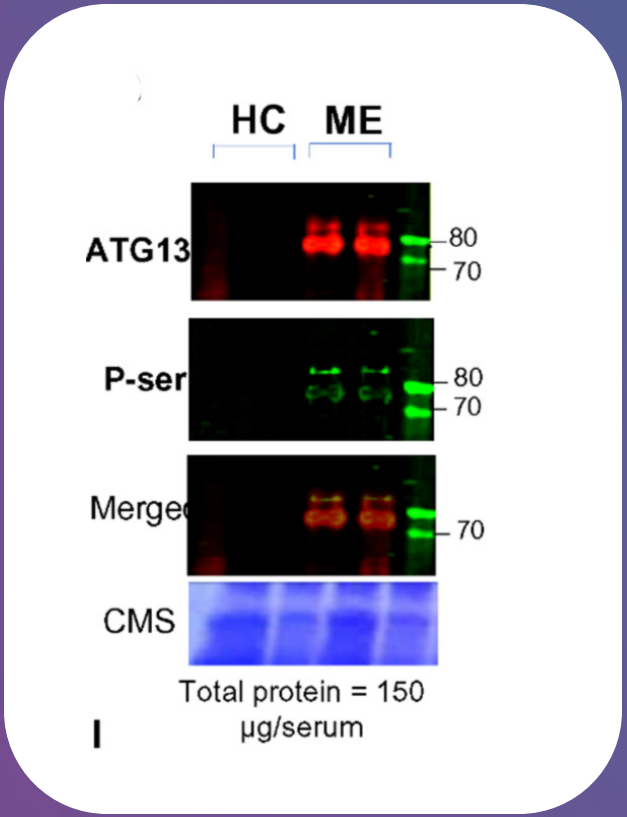
Scientific Premise

ATG13: A Key Factor for ME/CFS





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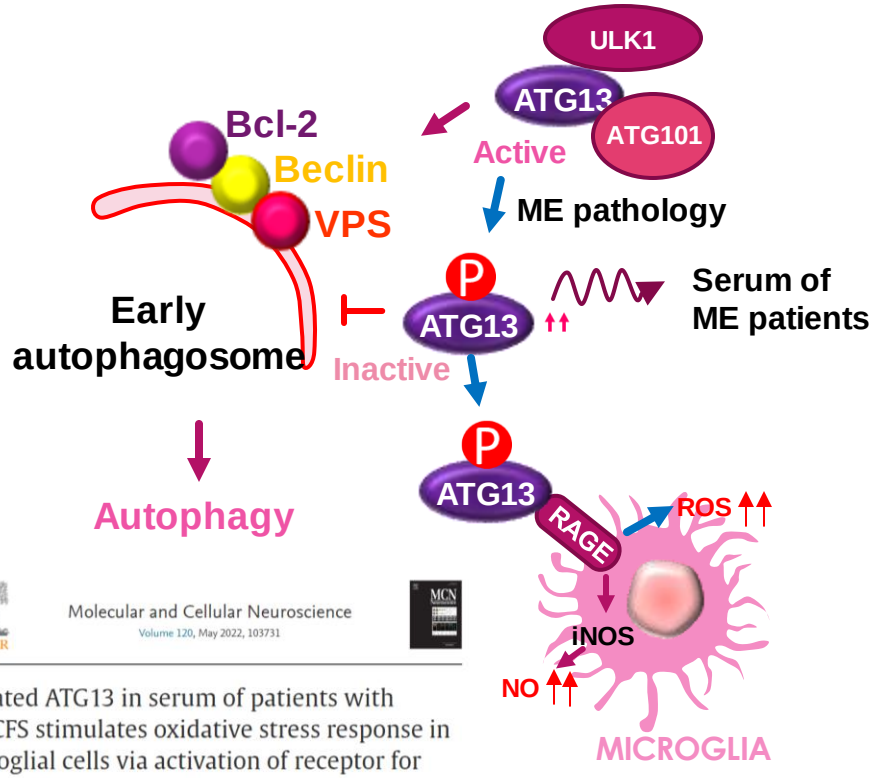
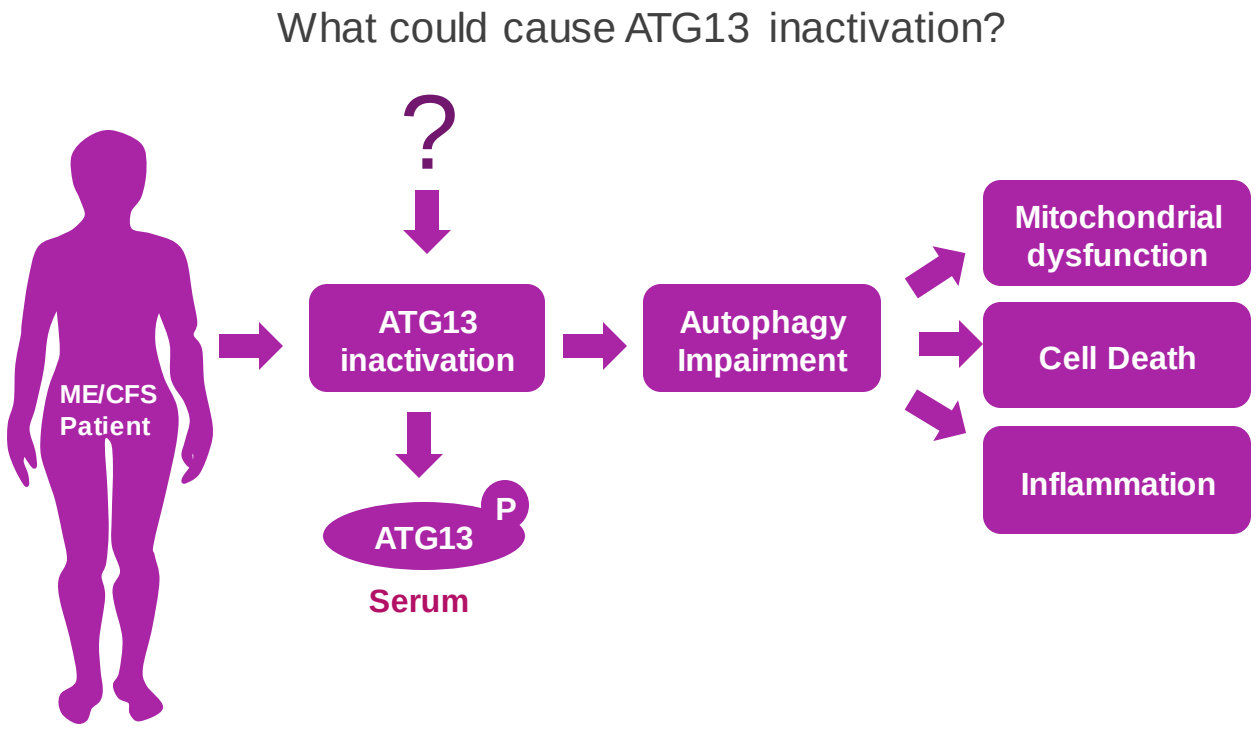
Molecular Mechanism?



Molecular and Cellular Neuroscience
Volume 120, May 2022, 103731

Elevated ATG13 in serum of patients with ME/CFS stimulates oxidative stress response in microglial cells via activation of receptor for advanced glycation end products (RAGE)

Gunnar Gottschalk [a, b], Daniel Peterson [a], Konstance Knox [c], Marco Maynard [b], Ryan J. Whelan [b], Avik Roy [a, b]



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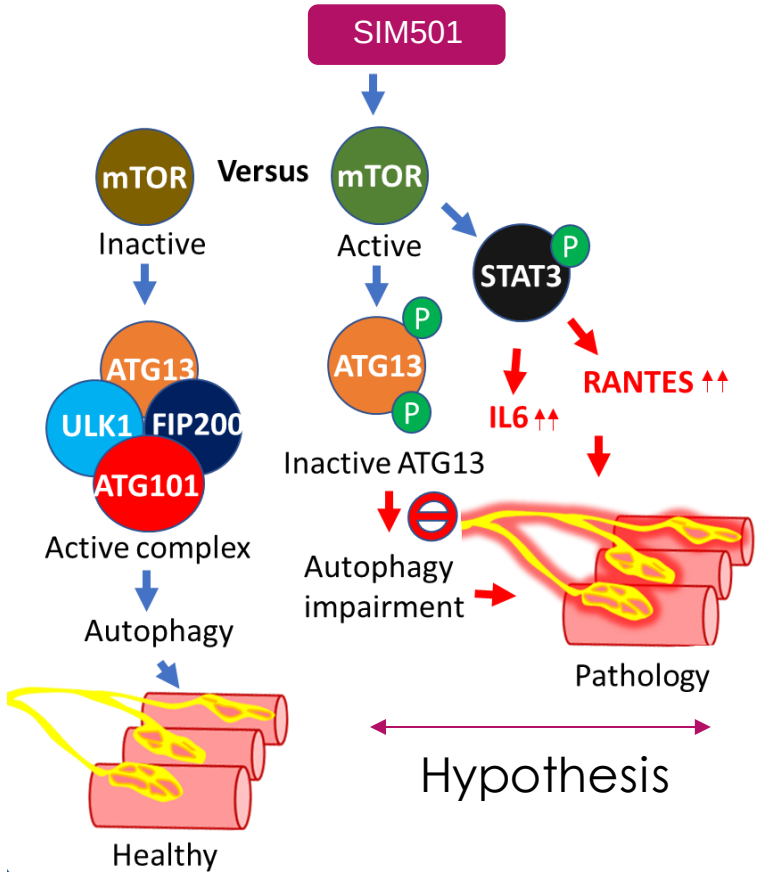
Activation of mTOR impairs ATG13



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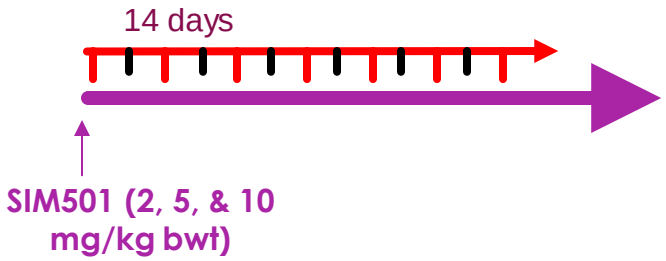
A strategy to create a drug-induced model



1. **Muscle fatigue** (EMG and grip strength)
2. **PEM** (comparisons between pre- and post-treadmill.
3. **Attention deficit and brain fog**

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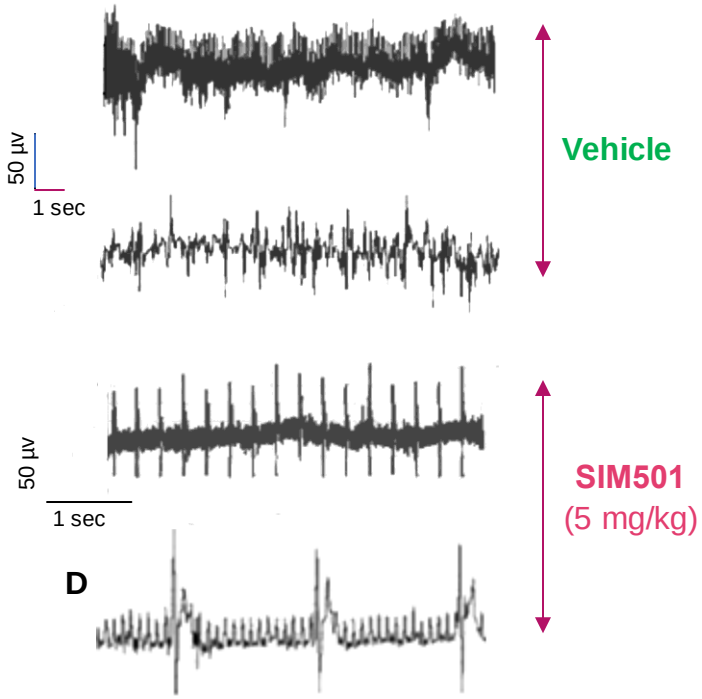
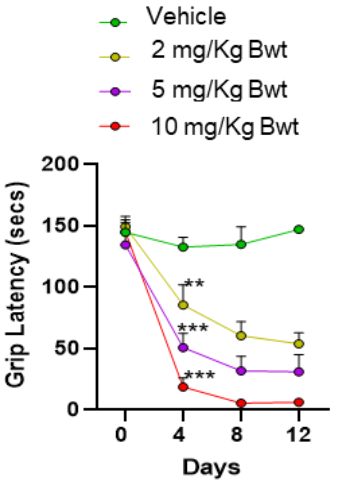
Functional inactivation of ATG13 causes severe muscle fatigue

A

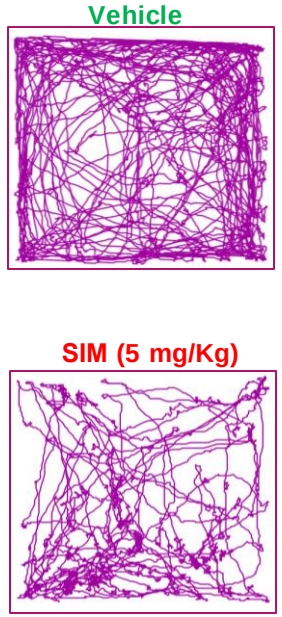
EMG



Grip strength



Gross movement



"Marching soldier" muscle wave = inflammatory demyelination

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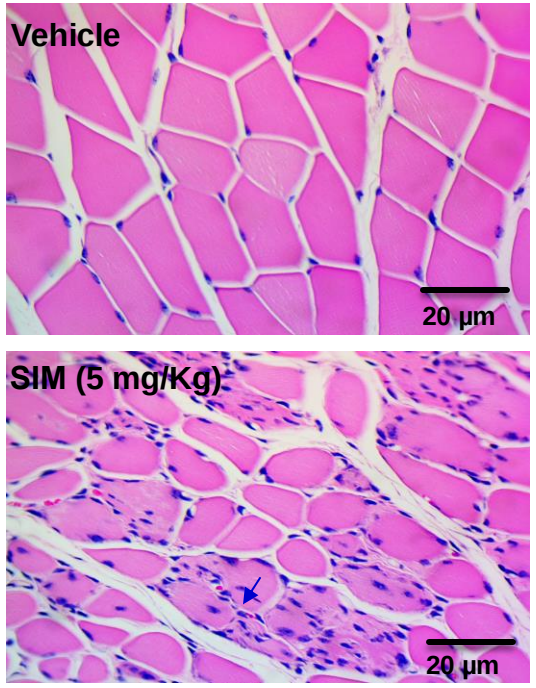
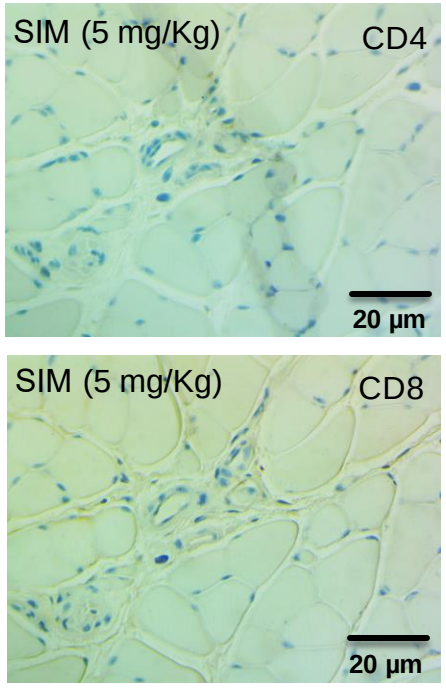
Inflammatory mononucleosis?

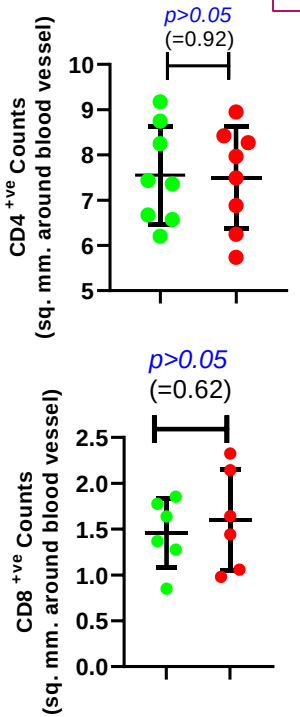
H&E

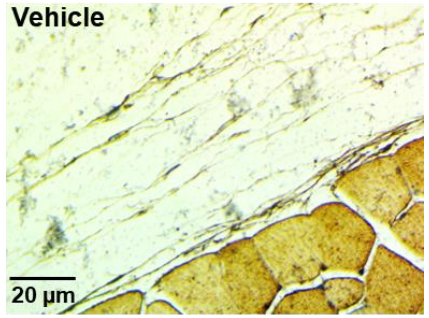


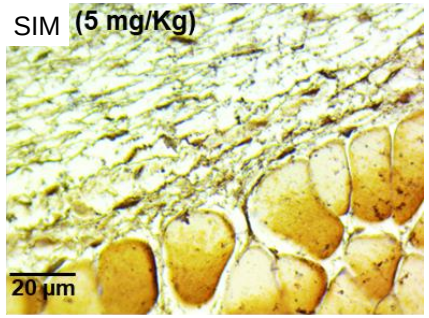
T cells

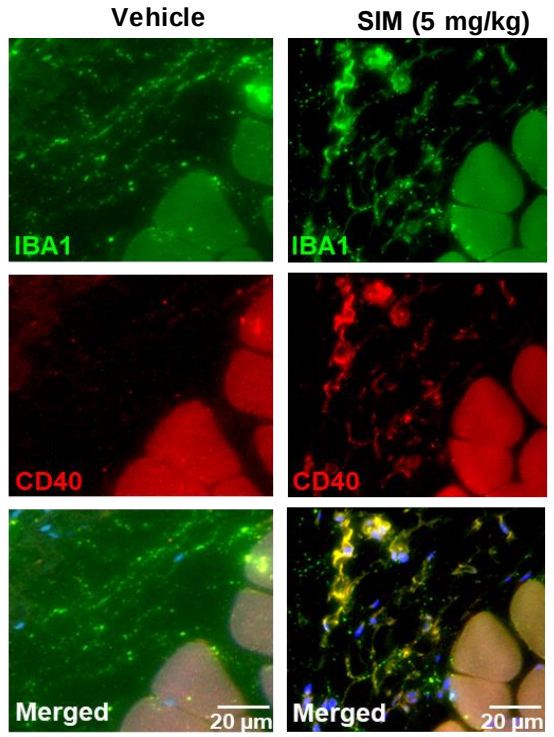


Macrophages (IBA1)









Macrophages (M1)

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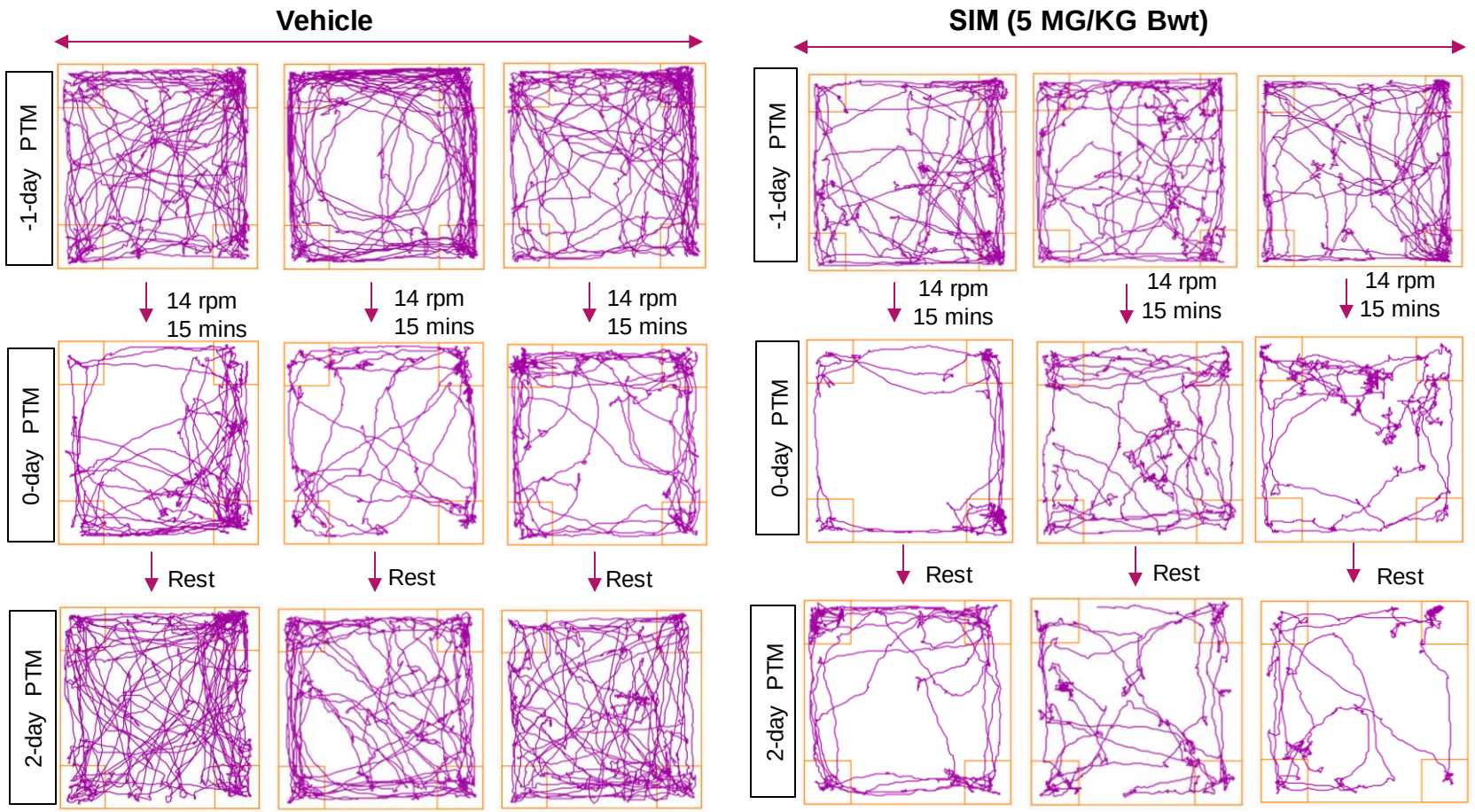
PEM study

OPEN Field study (Stoelting ANY Maze® app)



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To understand the direct role of ATG 13 and to make a stable model, atg13-null strain is required

Limitations to drug-induced mouse model

1. The fatigue is transient. Exists up to 1 month after the last dose.
2. The direct role of ATG13 is not clear.

Advantages of ATG13-null mouse model

1. The fatigue is expected o be stable.
2. The direct role of ATG13 will be established.

Disadvantages and confounding errors of ATG13-null mouse model

1. Growth deficit.
2. Cardiomyopathy
3. Homozygous mice do not survive

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Future Direction

Cre-Lox system to generate cell and tissue-specific mutation of atg13 gene in older mice

Muscle-specific mutation of ATG13 ($ATG13^{\Delta muscle}$)

Brain-specific mutation of ATG13 ($ATG13^{\Delta brain}$)

PNS-specific mutation of ATG13 ($ATG13^{\Delta PNS}$)

PNS = Peripheral nervous System

Expected results:

($ATG13^{\Delta muscle}$) = fatigue and PEM ?

($ATG13^{\Delta brain}$) = anxiety and attention deficit?

($ATG13^{\Delta PNS}$) = dysautonomia?

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Thank you!

NIH National Institute of Neurological Disorders and Stroke

Solve M.E.

UNIVERSITY of WISCONSIN UWMILWAUKEE

Coppe LABORATORIES

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Scientifically Redefining ME/CFS