

## Simmaron Research

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Driving Treatment Discovery  
for ME/CFS and Long-Covid

### OUR BOLD GOAL FOR ME AND LONG-COVID: Test and treat, not trial and error

#### 2025 PROGRESS

We found an impaired pathway in an ME subset: autophagy

We identified a biomarker to help diagnose it: ATG13

We demonstrated its correlation with PEM in mouse models

We are running successful treatment trials to restore  
autophagy: rapamycin

We are developing a test to predict who is likely to respond

...and our findings are being replicated!

**Double your gift  
up to \$500,000**



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## **Make a difference in the lives of people with ME and Long-Covid.**

As a non-profit, the Simmaron team needs your help making our community's dream come true: evidence-based treatments, and tests to predict who's likely to respond to them.

Other diseases have them—ME and Long-Covid should too.

# ATG13 and the First Mouse Model for PEM

## Publications

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)

International Journal of Molecular Sciences  
2023 May 13

Inactivation of ATG13 stimulates chronic demyelinating pathologies in muscle-servicing nerves and spinal cord

Immunologic Research  
2025 Jan 7

Low Dose Rapamycin Alleviates Clinical Symptoms of Fatigue and PEM in ME/CFS Patients via Improvement of Autophagy

Journal of Translational Medicine  
2025 Oct 21



### Step 1: Identified Target

In ME, we are the first to study autophagy, an essential cellular clean up process that rids cells of depolarized, dysfunctional mitochondria and other destabilizing waste.

We found that ATG13 was circulating in the blood instead of inside cells working to repair them, indicating autophagy disruption due to chronic activation of mTOR.

Malfunctioning autophagy results in significant cellular stress, immune activation, and insufficient supply of energy for the cell. It impairs mitochondria and sets off inflammatory processes.



### Step 2: Tested in Animal Model

Then our scientists developed mouse models to test defective autophagy and mTOR activation, in collaboration with the Milwaukee Institute for Drug Discovery at the University of Wisconsin Milwaukee.

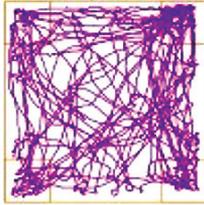
We created two different types of animal models from our ATG13 findings: a chemically induced model suppressing ATG13, and a transgenic model deleting ATG13.

The effect of suppressing or deleting ATG13 in study mice manifested post-exertional malaise “PEM”, the defining symptom of ME/CFS, and now we have the first disease-relevant mouse model for PEM.

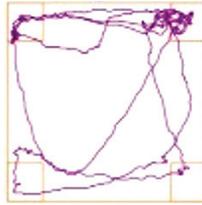
# Rapamycin Treatment Trial and Predictable Efficacy

## Mouse Activity Tracks

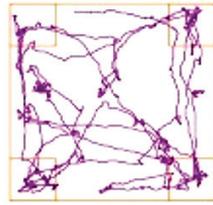
2 Days after treadmill



Normal activity pattern



Genetically deleted ATG13 activity pattern



Chemically suppressed ATG13 activity pattern



### Step 3: Treatment Trial for PEM

Our mouse models confirmed that mTOR activation could produce PEM through defective autophagy and that ATG13 could diagnose it. That set of findings led us to conduct treatment trials of an FDA-approved mTOR inhibitor, rapamycin, and track biomarker changes in tandem with clinical improvements.

This year, we published peer-reviewed findings from Phase 1 of our rapamycin observational trial in the prestigious *Journal of Translational Medicine*. This is a high honor for an ME treatment trial and Simmaron.



### Step 4: A Test to Predict Efficacy

**In a disease first, our *Journal of Translational Medicine* publication validates our steps to develop a biomarker test that can help predict who is likely to respond to rapamycin treatment. A test to replace trial and error!**

Our study model, designed for ME and LC patients, enables patients to participate from home. Our partnership with AgelessRx allows us to conduct this trial as a multi-centered, decentralized trial. Fundraising is currently supporting enrollment at no cost to patients.

## A BIG DEAL FOR ME AND LONG-COVID

# Biomarker-based Treatment

Remember when we said our ATG-13 findings were a big deal? Now we can show you why. Our peer-reviewed findings show:

### REDUCED POST-EXERTIONAL MALAISE AND IMPROVED SYMPTOMS

Responders reported fewer and less severe PEM events, increased energy, reduced fatigue, improved cognition, and reduced orthostatic intolerance.

### A BIOMARKER: PREDICTING RESPONDERS IN CLINICAL TRIALS

Beyond trial and error. Clinical improvement correlates with our biomarkers of autophagy dysfunction, pATG13 and Beclin-1.

#### Next Steps

- Phase 2 is well underway to study response and biomarker data over a longer time period.
- Planning a placebo-controlled trial to prove efficacy and validate our predictive diagnostic test.
- Developing this diagnostic for clinical use.



**Double your gift up to \$500,000**

Help us develop a test to predict who's likely to benefit from rapamycin and fund a placebo-controlled trial.

**DONATE NOW**

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Dr. Gunnar Gottschalk, CEO and Section Chief, Translational Science, and  
Dr. Avik Roy, Chief Scientific Officer and Section Chief, Neurobiology.

**Thank you for supporting our science, from all of  
us at Simmaron Research.**

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948 Incline Way  
Incline Village, NV 89451  
[www.simmaronresearch.com](http://www.simmaronresearch.com)

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