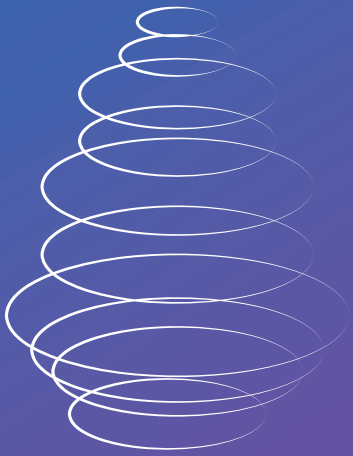


Simmaron Research

Driving Treatment Discovery for ME/CFS and Long-Covid

Studying Patients

Defining Subsets

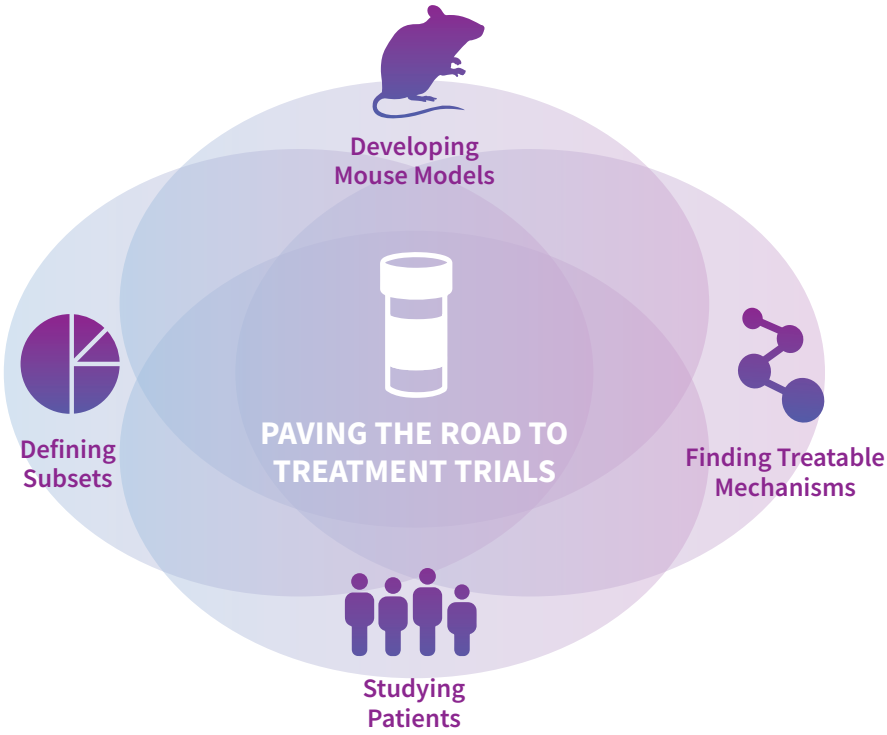
Developing Mouse Models

Finding Key Mechanisms

We want treatment for ME/CFS and Long-Covid.

Simmaron Research is a 501(c)(3) nonprofit

At Simmaron, we are...



Simmaron's mission is to change the game for ME/CFS and Long-Covid drug research.

We are resolving key roadblocks that prevent our entire research community from moving forward: poorly defined subsets and a lack of an animal model.

These key components will not only enable our team to develop treatments, it will blow the door open for outside researchers and pharmaceutical companies to invest in ME/CFS and Long-Covid research.

Mouse Models Will Change Everything

"This is incredibly significant — without a mouse model, drugs can't be tested. We haven't seen anything like this before."

The SolveME Initiative

Diseases with mouse models have active drug pipelines. Think about Parkinson's disease, Alzheimer's, and multiple sclerosis.

Simmaron Research is developing the 1st ME mouse models to find treatable pathways and fill this longstanding gap in research.

Our mouse model for ME/CFS is so much bigger than just us. It will widen the pool of researchers for ME, and encourage investment by big pharmaceutical companies. It will create a new playing field to spur discoveries — a foundational platform for future breakthroughs. And importantly, mouse models will help our disease meet stringent requirements for FDA approved treatment trials.

So we've teamed up with the Milwaukee Institute for Drug Discovery at the University of Wisconsin to generate mouse models that display the cardinal symptoms of ME and Long-Covid.

Mouse Models for ME: a drug-development must

A mouse model for PEM? Brain fog? POTS?

Imagine a mouse that takes days or weeks longer to recover from running – a mouse with post-exertional malaise (PEM).

Our goal is to show that broken pathways in patients with ME or Long-Covid translate into mouse models for PEM, brain fog or POTS.

If we can demonstrate these core symptoms and reverse them in mouse models, we can identify potential treatments and attract interest from pharmaceutical companies to invest in treatment trials.

Simmaron is combining disease understanding, experience in finding treatable molecular mechanisms in other diseases, and experts in animal modeling to breakthrough to treatments.

We are creating a mouse model for each of the major symptoms in ME/CFS:

PEM **POTS** **Brain Fog**

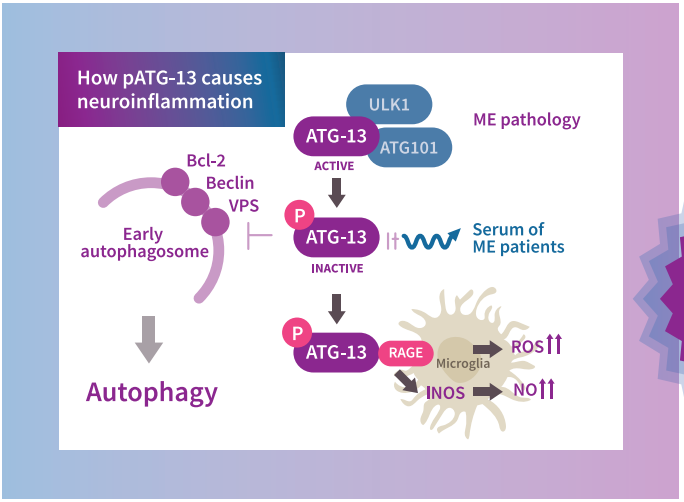
EVERY GIFT SUPPORTS OUR RESEARCH

Donate to the mouse model project and make change for ME/CFS and LC!

www.simmaronresearch.com/donate

Trail-blazing New Findings

The Science Behind the Mouse Model: ATG-13



2023
NIH R21
Grant Winner

Simmaron Wins First NIH Grant to Study ATG13

We are the first to study autophagy in ME/CFS patients, and the trail-blazing has paid off. Dr. Roy PhD and Dr. Gottschalk PhD have been awarded a competitive R21 grant from the National Institutes of Health for our study “ATG13: A new player in ME/CFS.”

This ATG-13 study will help Simmaron’s team to develop a targeted pathway for treating neuroinflammation found in diseases like ME/CFS, POTS, and Long-Covid. ‘Autophagy’ is the critical waste-removal process of the cell that we have shown to be dysfunctional in ME/CFS patients.

ATG-13 should be inside cells, prompting autophagy. But we found ATG-13 in blood and setting off inflammatory molecules in the brain.

We believe we have found a critical pathway involved in post-exertional malaise (PEM), the hallmark symptom of ME/CFS.

The Role of BH4 in ME/CFS

BH4 has never been studied in ME/CFS before. BH4 is critical for the synthesis of neurotransmitters, such as dopamine and serotonin. It's known to be tightly coupled with cardiovascular health and circulation.

When we looked at our patients' serum, we observed that there was a strong upregulation of BH4 in ME patients compared to healthy controls. ME patients who also had Orthostatic Intolerance had an even higher level of BH4 in serum.

In this instance, more is definitely not better. Though the role of BH4 in health and disease is not fully understood, we do know dysregulated BH4 biosynthesis impairs mitochondrial energy production, induces oxidative stress, and augments autophagy impairment. It has also been linked to reduced blood pressure.

This biological pathway has excellent potential for pharmaceutical treatment.

Five Peer-Reviewed Publications in 2023

1. New science: "ATG13: A new player in ME/CFS"

2. "Detection of Elevated Level of Tetrahydrobiopterin in Serum Samples of ME/CFS Patients with Orthostatic Intolerance: A Pilot Study"

3. Collaboration: "Proteomics and cytokine analyses distinguish myalgic encephalomyelitis/chronic fatigue syndrome cases from controls"

4. Collaboration: "Deficient butyrate-producing capacity in the gut microbiome is associated with bacterial network disturbances and fatigue symptoms in ME/CFS"

5. "Potential molecular mechanisms of chronic fatigue in LongCOVID and other viral diseases"

Our Track Record of Game-Changing Science for ME/CFS

Defining Subsets

Simmaron's collaborations with leading researchers have identified multiple subsets of patients differentiated by science. Our 2015 study with Drs. Lipkin and Hornig identified early and longer duration patients with distinct, and somewhat opposing, immune patterns.

Our signature spinal fluid studies identified classical and atypical "Peterson Subset." Our microbiome collaboration with Dr. Lipkin's NIH Research Center separated ME/CFS patients with Irritable Bowel Syndrome from those without, through bacterial patterns. Subsets are a key to successful treatment trials.

8 Subsets Defined by Simmaron

- Early duration
- Longer than 3yrs sick
- Classical
- Atypical Peterson Subset
- ME with IBS
- ME w/o IBS
- BH4 in ME
- BH4 in ME w/OI

Biobank Ripe for Discovery

Simmaron has a deep, well-characterized biobank of samples spanning four decades of ME/CFS clinical research, with extensive clinical records to be mined. Our team is the only clinical team to be active during both the Lake Tahoe outbreak of ME/CFS and the COVID-19 pandemic, now with biological samples from both.

Over three decades of biological samples and records from approximately 1,000 ME/CFS patients

Since our inception:

2023 NIH R21 Grant

2022 Ramsay Grant

2016 Ramsay Grant

Trained more than a dozen young scientists as interns

Led data analysis of potential treatments

Best-in-class collaborations with:

- NIH Research Centers
- Centers for Disease Control (CDC)
- Columbia University
- Cornell University
- Stanford University
- Griffith University
- University of Wisconsin Milwaukee

Funded over **$4.5 million** of ME research

5 New peer-reviewed publications in 2023 alone

29 Peer-reviewed publications

Who We Are

Dr. Daniel L. Peterson, MD

Simmaron is rooted in the medical practice and leadership of Daniel L. Peterson, MD, who has been providing clinical care, running treatment trials, and building a one-of-a-kind biobank for ME/CFS patients since the Tahoe outbreak in 1984.

Dr. Peterson is a founding member of Simmaron Research's Scientific Advisory Board, and his clinical insight has attracted top scientists to ME research and directly contributed to identifying subsets.

A New Generation of Scientists

Dr. Avik Roy, PhD

Simmaron Chief Scientific Officer

Dr. Roy is known for his success finding treatable pathways in Parkinson's and Alzheimer's. He has published over 75 peer-reviewed manuscripts, won Rapid Response Innovation Award from Michael J. Fox Foundation, Young Investigator Award by American Society for Neurochemistry, Ramsay Award by Solve ME, and now Simmaron's first NIH grant to further our autophagy and mouse model work.

Dr. C. Gunnar Gottschalk, PhD

Simmaron Executive Director and PI

Dr. Gottschalk has a PhD in neuroscience on top of extensive experience conducting clinical research in the ME/CFS field, collaborating with the CDC, NIH Research Centers, and renowned clinicians and scientists. He is uniquely trained to drive Simmaron's research focus on treatment discovery.

Scientific Advisory Board

Dr. Daniel Peterson, MD, Sierra Internal Medicine
Dr. Konnie Knox, PhD, Coppe Laboratories
Dr. Maureen Hanson, PhD, Cornell University
Dr. Mady Hornig, MA MD, Columbia University
Dr. Paul Guyre, PhD, Dartmouth University

Collaboration with Milwaukee Institute for Drug Discovery

Simmaron's new lab is located in the animal facility at the University of Wisconsin Milwaukee.

We are teaming up with the Milwaukee Institute for Drug Discovery at UWM to allow our scientists to translate findings from human samples collected from both ME/CFS and Long-Covid patients into the first mouse models of both diseases.

We are honored to be working with Dr. Linda Adrienne Allen, DVM, Attending Veterinarian at UWM and Dr. Alexander "Leggy" Arnold, Professor of Chemistry at University of Wisconsin Milwaukee and Director of Milwaukee Institute of Drug Discovery.

Sign up for email updates:
www.simmaronresearch.com/signup

"ME/CFS is no more difficult to unravel than diseases like Parkinson's and MS. By focusing on bringing a mouse model to ME/CFS, we are well on our way to bringing you treatment."

Dr. Avik Roy, PhD
Chief Scientific Officer, Simmaron Research

Simmaron Research
Driving Treatment Discovery
for ME/CFS and Long-Covid

948 Incline Way,
Incline Village, NV 89451
www.simmaronresearch.com

Simmaron Research is a 501(c)(3) nonprofit