

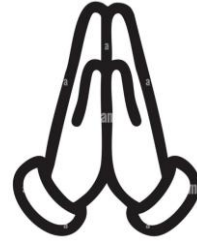
A Safe, Accessible Treatment for ME/CFS? The Mitochondrial Stabilizer IVO-21 Study

Presentation for Solve ME/CFS
(September 8, 2026)

Jay H. Chung MD, PhD
Laboratory of Obesity and Aging Research
NHLBI, NIH



Thank you, SOLVE ME/CFS



Diseases

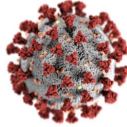
- 1. Acute: heart attack, stroke...**
- 2. Chronic: diabetes, cancer, hypertension...**

Illnesses

- 3. Acute: food poisoning, flu...**
- 4. Chronic: Normal tests, imaging studies..**

ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome)

Long COVID



infection

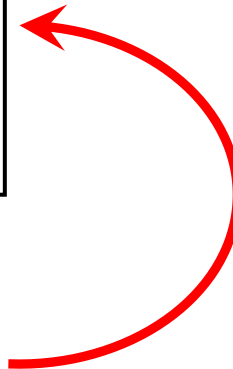


Illness

1. Pain
2. Post-exertional malaise (crash)
3. Fatigue
4. Brain fog
5. Insomnia
6. Dizziness/POTS



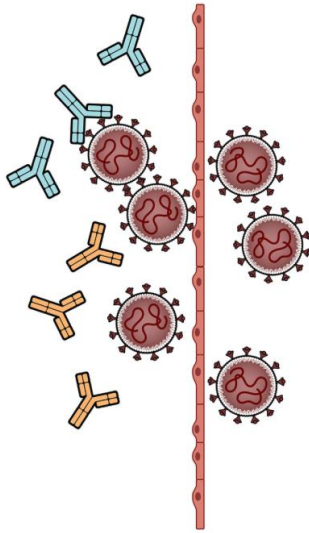
recover



relapse

Infection-immune theories of ME/CFS and long COVID

A sustained or renewed sensing of immune stimuli



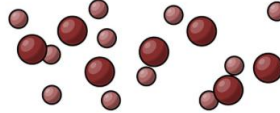
1 Viral reservoir

Persistence of ongoing viral replication at sites difficult to clear

Viral RNA



Nucleocapsid and other viral proteins



Spike protein

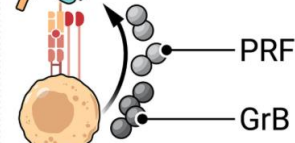


2 Viral fragments

Viral RNA and proteins, such as spike protein, can serve as a source of persistent antigen

Increased killing of healthy cells

Autoantibodies target self-antigens

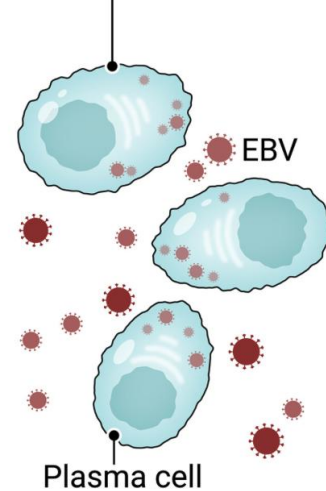


Autoreactive CD8⁺ T cell (effector)

3 Autoreactivity

Recognition of autoantigens where the immune system mistakenly attack self; this can also lead to autoimmune diseases

EBV reactivation



4 Transcriptional activation or reactivation of latent viruses

Perceived as a new or ongoing threat

Anti-virals are not effective ME/CFS or long COVID

Clinical Therapeutics/Volume 41, Number 5, 2019

Commentary

Pharmaceutical Interventions in Chronic Fatigue Syndrome: A Literature-based Commentary

Spencer Richman, B.Sc.^{1,2}; Matthew C. Morris, Ph.D.^{1,2};
Gordon Broderick, Ph.D.^{1,2,3,5}; Travis J.A. Craddock, Ph.D.^{3,4,6};
Nancy G. Klimas, M.D.^{3,6}; and Mary Ann Fletcher, Ph.D.^{3,6}

¹Gosnell School of Life Sciences, Rochester Institute of Technology, Rochester, NY, USA;
²Center for Clinical Systems Biology, Rochester General Hospital, Rochester, NY, USA;
³Institute for Neuro Immune Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA; ⁴Departments of Psychology and Neuroscience, Computer Science, Nova Southeastern University, Fort Lauderdale, FL, USA; ⁵Department of Biomedical Engineering, Rochester Institute of Technology, Rochester, NY, USA; and ⁶Department of Clinical Immunology, Nova Southeastern University, Fort Lauderdale, FL, USA



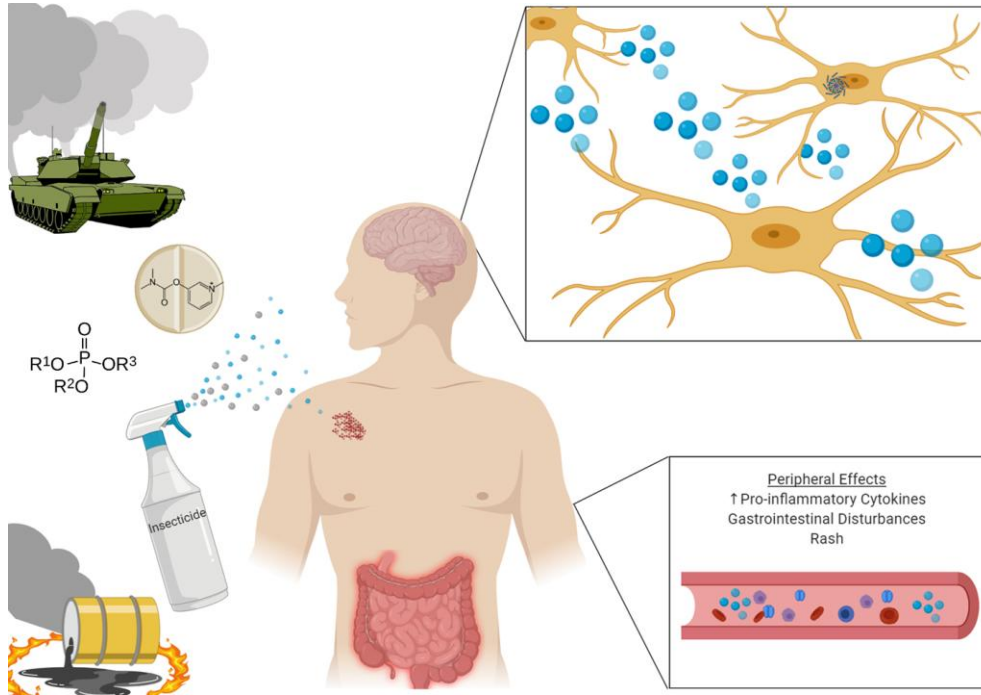
Nirmatrelvir-ritonavir targeting viral persistence in post-COVID-19 condition (long COVID) in the USA (RECOVER-VITAL): a randomised, double-blind, placebo-controlled, phase 2 trial

Lindsey R Baden, Nirav S Shah, Sean T H Liu, Jonathan Cohen, James May, Andre Kumar, Grace A McComsey, Peter Chen, Michelle Floris-Moore, Nora G Singer, Inti Fernandez, Alex J Slandzicki, Zanthia Wiley, Alexandra Kadl, David A Kaminsky, Harvey Hsu, Tiffany A Walker, Aluko A Hope, Luis Ostrosky-Zeichner, Jason D Goldman, Michael J Peluso, Thomas F Patterson, Sairam Parthasarathy, Janet M Mullington, Paul Bolin Jr, Sarah E Jolley, Jerry A Krishnan, Mario Castro, Sally L Hodder, Priscilla Pemu, Helen Y Chu, Michael G Risbano, Maya R Jerath, Eleftherios Mylonakis, Ryan T Hurt, Radica Alicic, Nabila S Azad, Marc A Sala, Michelle S Harkins, Jeffrey Parsonnet, Neil Stafford, Philip Robinson, Sabiha Hussain, Xian Qiao, Sophie Two Hawk, Michael Lillestol, Nathan Erdmann, Kelly A Gebo, Praveen Sudhindra, Joseph Sassine, Gailen D Marshall, Tulika Chatterjee, Caryn G Morse, Eyal Kedar, William W Stringer, Jennifer A Frontera, Michael Jordan, Caitlin Blaskewicz, Jorge L Santana, Rachel A Foot, Cherry Wongtrakool, Matthew William McCarthy, Alem Mehari, Arch Amon, Alison K Cohen, Nita Jain, Christine Maughan, Doug Lindsay, Rachel Olson, Samuel Broderick, Pearl Rowe, Sean M O'Brien, David R Walt, Bruce D Levy, Leonard A Jason, Phillip A Low, Cyndya A Shibao, Barry Make, Lucinda Bateman, Susan Redline, David Knopman, Adrian F Hernandez, Tracy L Nolen, Craig Reist, Lisa Berdan, Richard Whitley, Kanecia O Zimmerman; for the RECOVER-VITAL Clinical Trial Group*



Is Gulf War Syndrome ME/CFS?

(250,000 out of 750,000 soldiers, primarily army)



1. What is Gulf War Illness

Chronic multi-symptom illness may include symptoms such as

-
- Pain
 - Cognitive difficulties and headaches
 - Fatigue
 - Gastrointestinal distress
 - Sleep issues
 - Respiratory problems
 - Joint and muscle pain
 - Skin problems

Treatment has focused on treating the symptoms and not the underlying causes, which are still poorly understood.

Exposure in 1990: It is unlikely that there is a toxin reservoir after >35 years

'Havana syndrome' and the mystery of the microwaves

8 September 2021

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Gordon Corera

Security correspondent, BBC News



BBC

There are diverse triggers unrelated to infection (20%): surgery, psychological trauma, ICU..

ME/CFS likely extends beyond a purely post-infectious phenomenon.

ME/CFS may reflect an underlying vulnerability to cellular stress in susceptible individuals.

Our goal is to define the biological basis of this vulnerability and leverage that understanding to develop effective therapies.

Many Treatments Have Been Tried—But None Has Yet Solved ME/CFS or Long COVID

Treatments that have been tested:

Immune therapies

Rituximab • IVIG • anti-inflammatory drugs

Blood flow & autonomic therapies

Pyridostigmine • beta blockers • fluids and salt

Energy & mitochondrial approaches

CoQ10 • metabolic therapies • supplements

Antiviral therapies

Paxlovid and other antiviral approaches

Symptom-directed treatments

Low-dose naltrexone • antihistamines •
rehabilitation • pacing

Metabolic therapies that have been tried

Approach	Basic rationale
CoQ10	Support mitochondrial electron transport
NAD ⁺ precursors	Increase NAD ⁺ availability for mitochondrial metabolism
Ribose	Provide substrate for nucleotide/ATP synthesis
Acetyl-L-carnitine	Facilitate fatty-acid transport into mitochondria
D-ribose + CoQ10	Support ATP production
Metformin Low dose rapamycin	Alter cellular metabolism and inflammatory signaling
Mitochondrial supplements	Attempt to improve oxidative phosphorylation
Dietary/metabolic interventions	Alter fuel utilization

different perspective on chronic illnesses

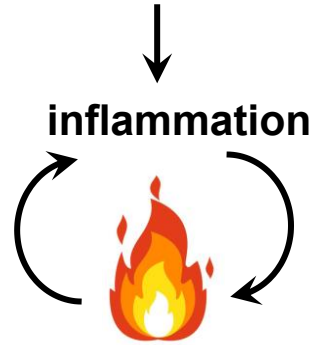
Key question: Regardless of how the “fire” was initially started, what keeps the fire going?

Positive feedback loop (vicious cycle)



Inflammation: fuel to the fire

Stressor
(e.g. infection, physical or psychological trauma...)



Byproduct of cellular damage
?

Molecular Mechanisms of Neuroinflammation in ME/CFS and Long COVID to Sustain Disease and Promote Relapses

Warren Tate^{1,2*}, Max Walker¹, Eiren Sweetman^{1,3}, Amber Helliwell¹, Katie Peppercorn^{1,2}, Christina Edgar¹, Anna Blair⁴ and Aniruddha Chatterjee⁵

HYPOTHESIS AND THEORY
published: 25 May 2022
doi: 10.3389/fneur.2022.877772



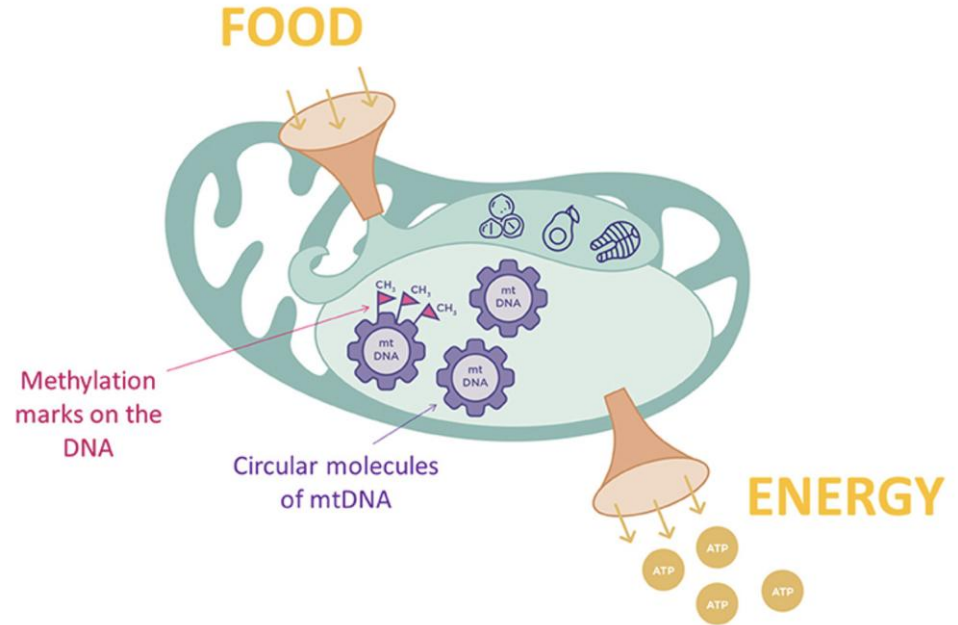
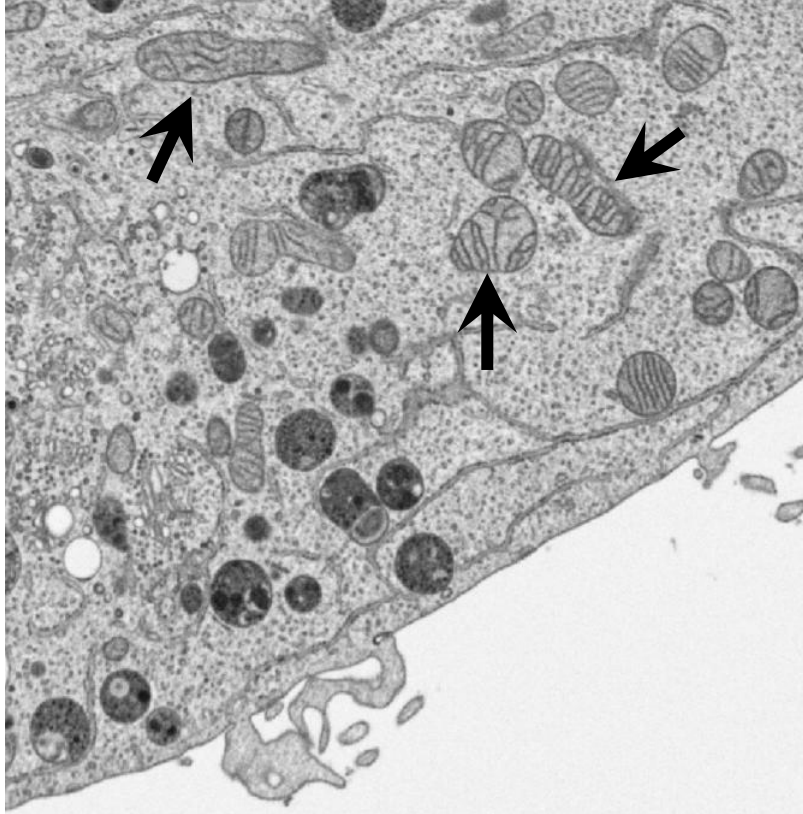
**Will not be detectable in a blood test-
Too diluted by the time it gets to your arm**



1979

Could there be an enemy within?

Mitochondria convert food into energy

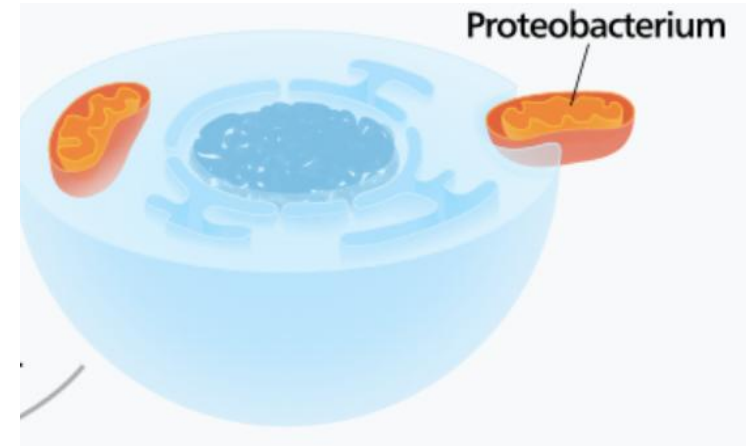
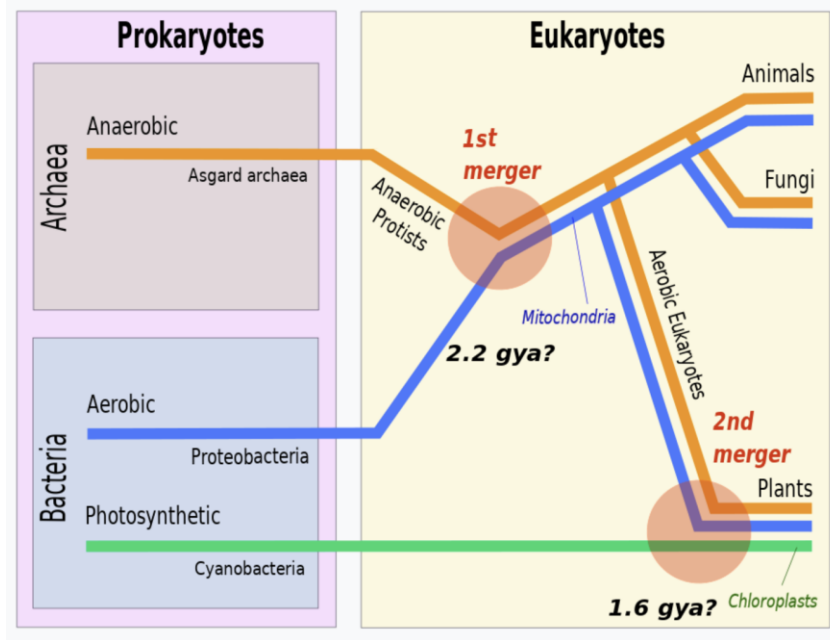


Dysfunctional mitochondria = broken metabolic engine



That mitochondrial dysfunction causes fatigue is obvious,
but how does it cause inflammation?

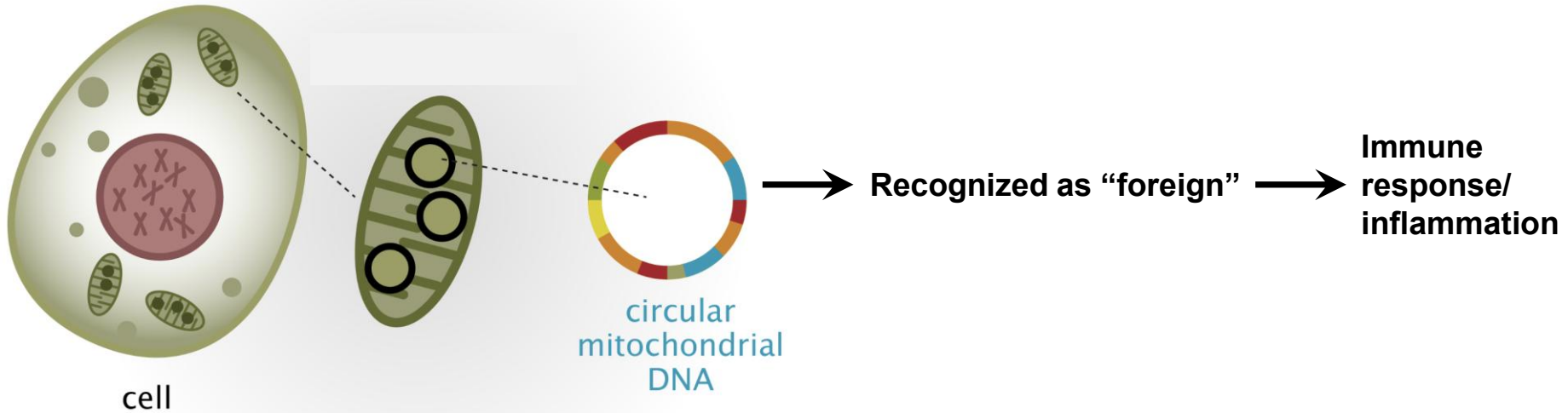
Mitochondrion is derived from proteobacteria (endosymbiosis)



Rickettsia prowazekii

Mitochondrial DNA (mtDNA) is different from our chromosomal DNA and our immune system recognizes it as foreign if it is released from mitochondria

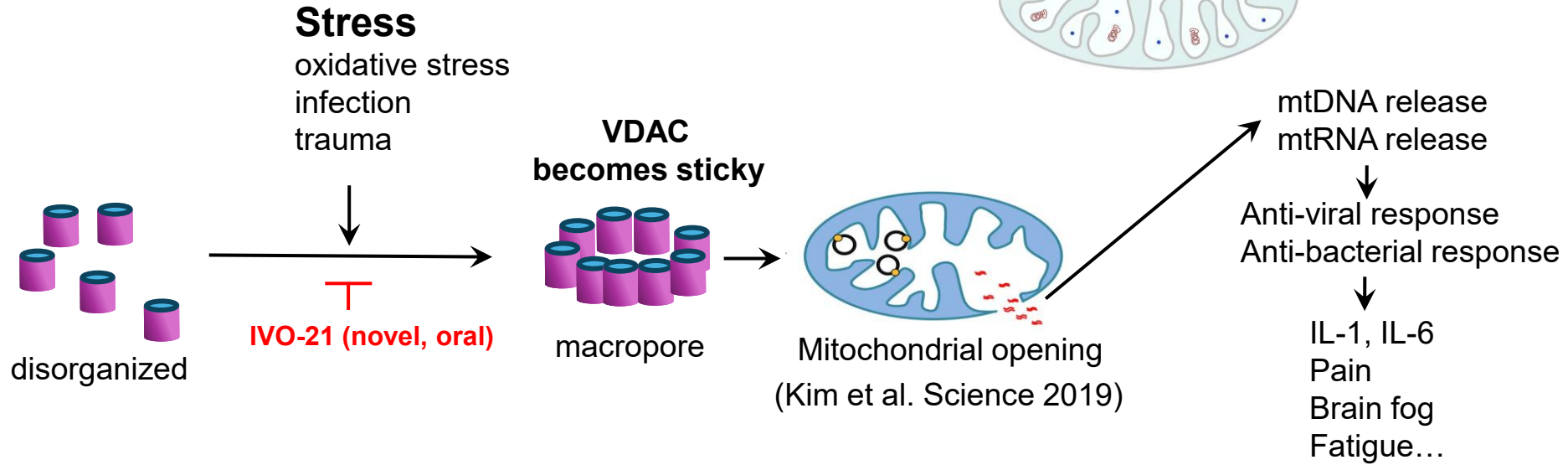
Mitochondria has bacteria-like DNA



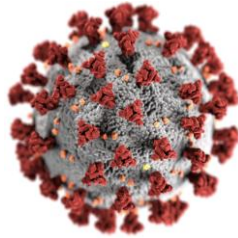
(c) CMG, UZ Brussels, Belgium

Mitochondrial membrane protein VDAC links stress to inflammation

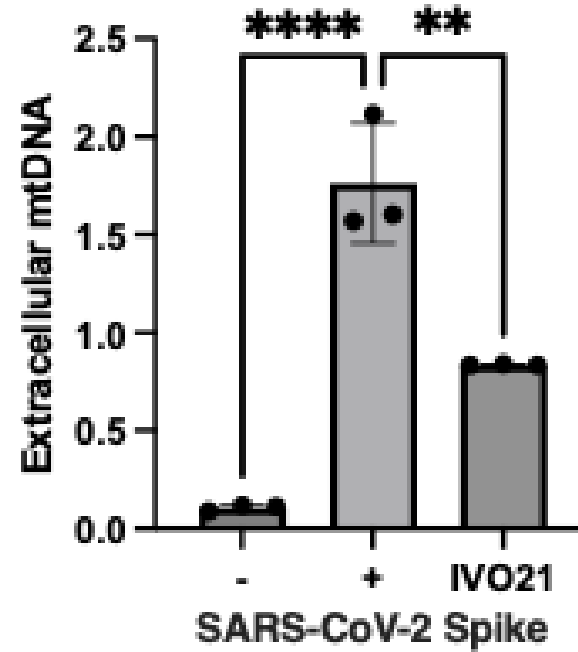
VDAC (voltage-dependent anion channel)



IVO-21 inhibits COVID-19 spike protein-induced ROS and mtDNA release



Covid 19



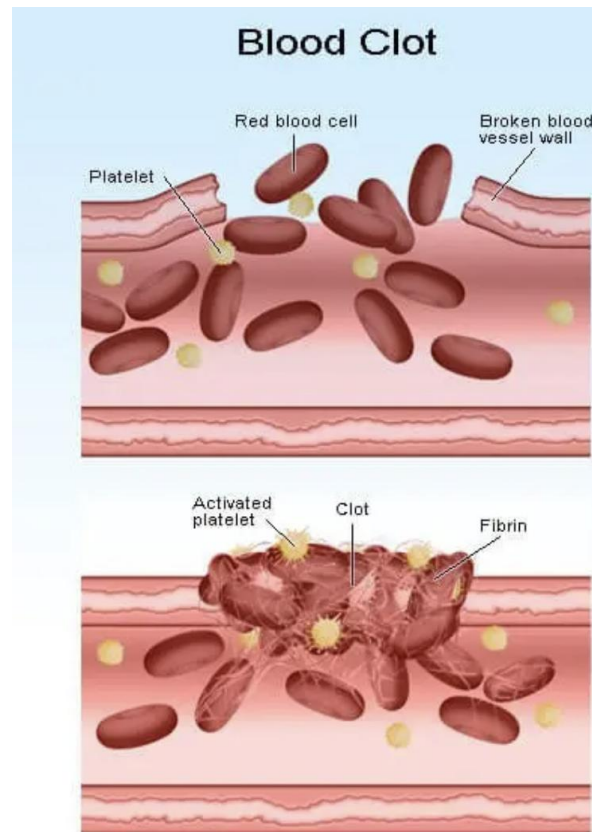
Received: 7 February 2023 | Revised: 18 March 2023 | Accepted: 10 April 2023

<https://doi.org/10.1016/j.jtha.2023.04.039>

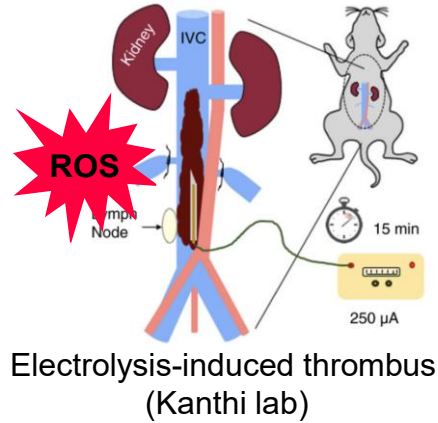
REVIEW ARTICLE

Thromboinflammation in long COVID—the elusive key to postinfection sequelae?

Leo Nicolai^{1,2} | Rainer Kaiser^{1,2} | Konstantin Stark^{1,2}



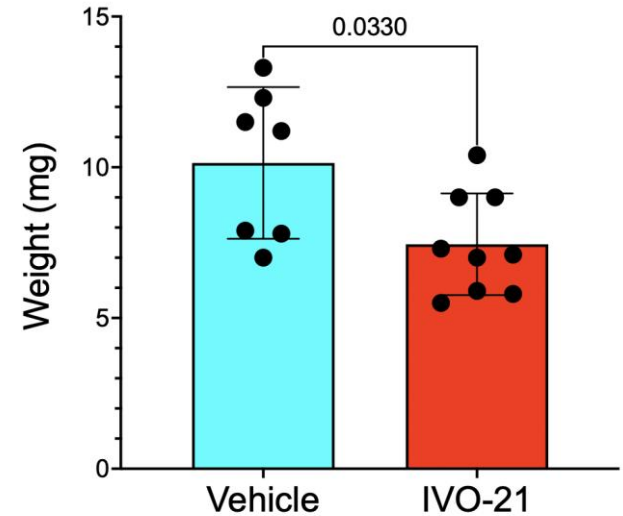
IVO-21 protects against thromboinflammation in mice without bleeding risk



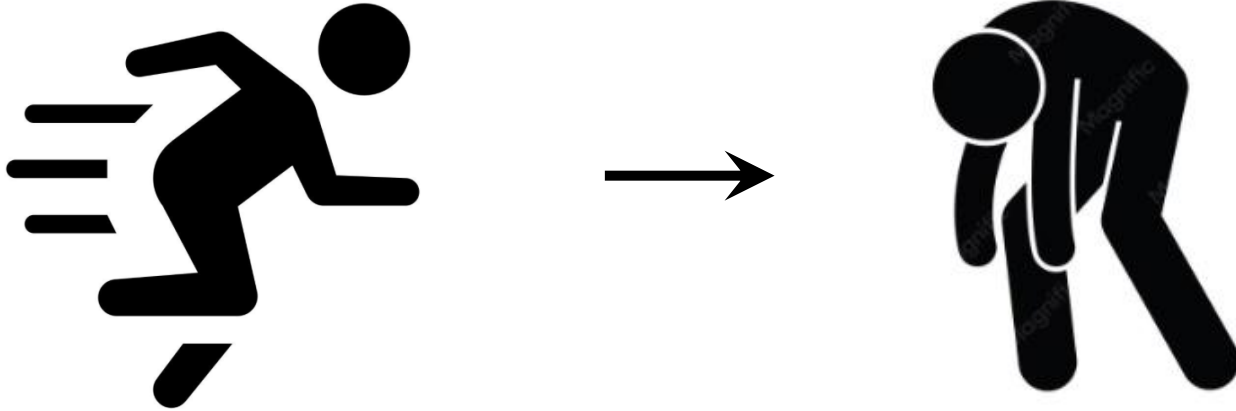
vehicle



IVO-21

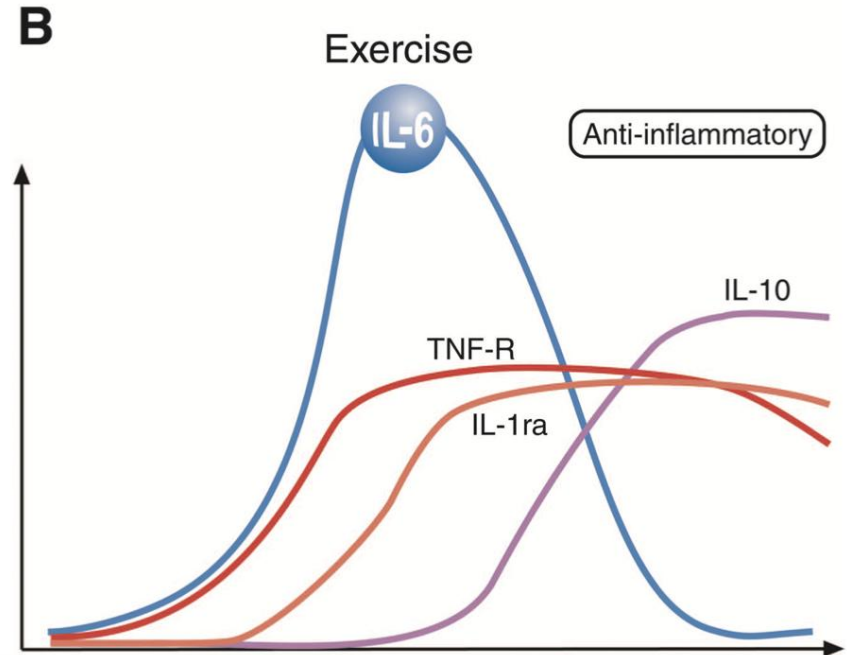
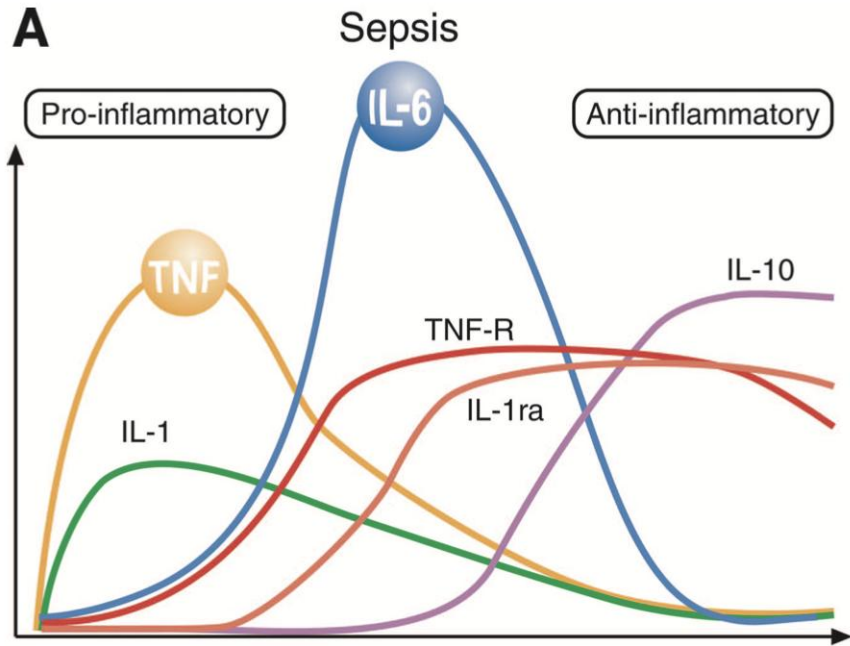


Does the inflammation cycle explain post-exertional malaise (crash)?



Physical or mental exertion

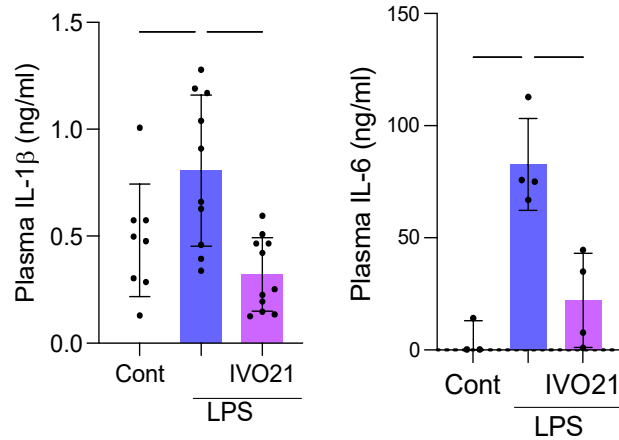
Inflammatory cytokine IL-6 is elevated in Long Covid in the resting state (could IL-6 explain post-exertional malaise?)



IL-6 is elevated after both sepsis and exercise

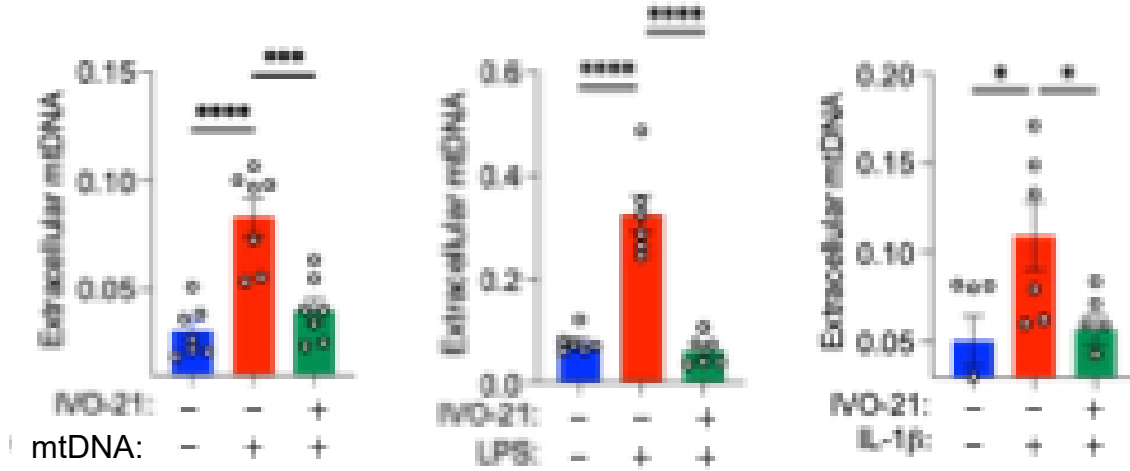
IVO-21 mitigates the inflammation cycle

mice

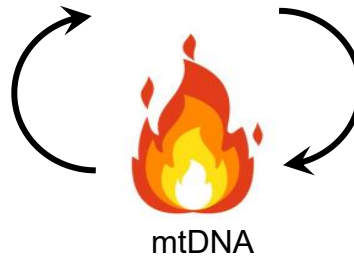


LPS=bacterial cell wall lipid

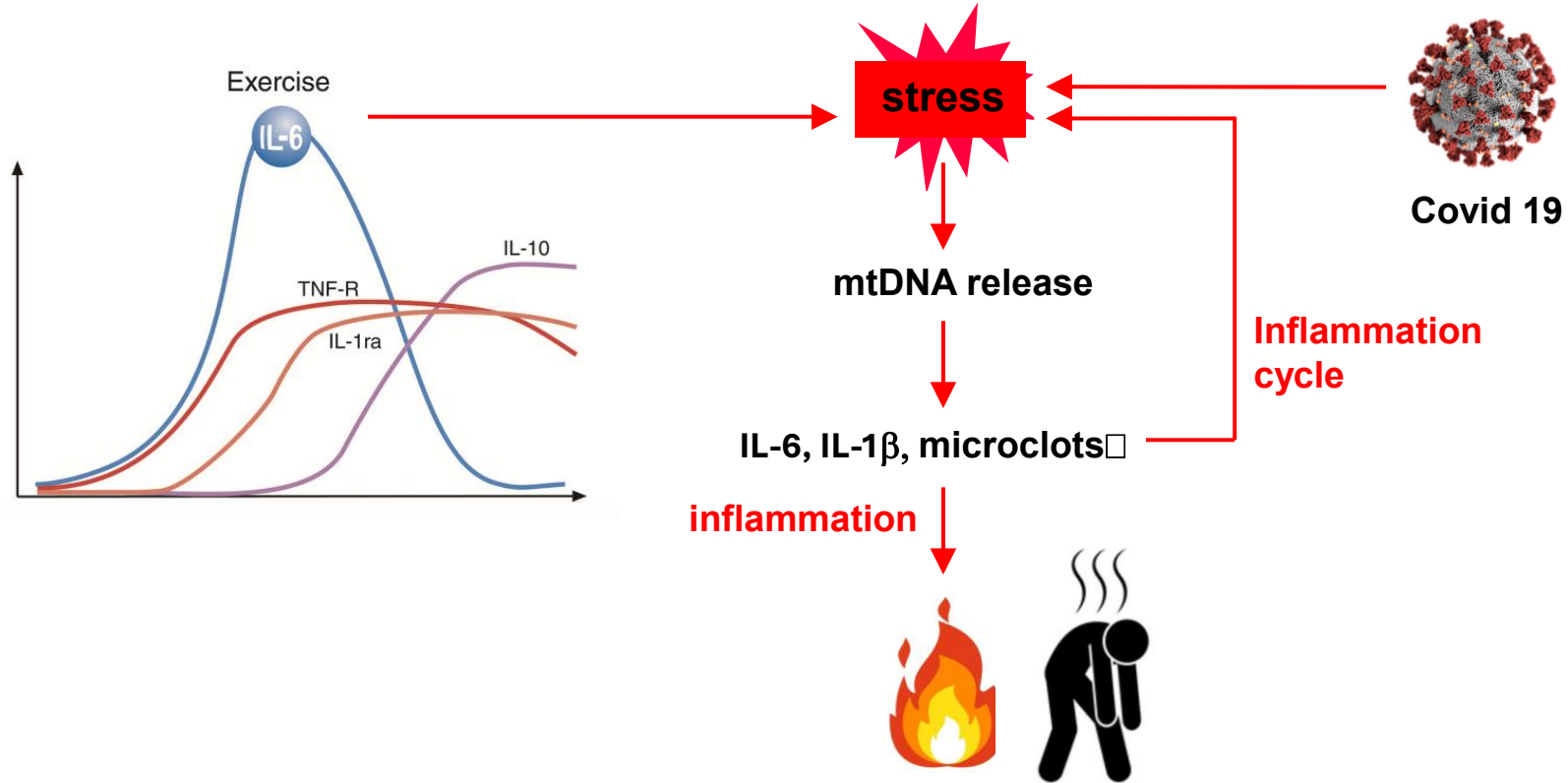
Human cells



inflammation/cell damage



Post-exertional IL-6 drives malaise in a vicious cycle?



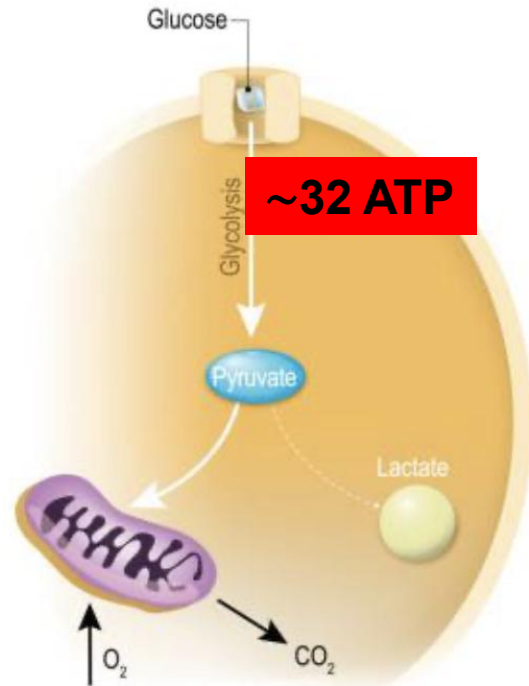
Different ways of making energy: marathon runner vs sprinter



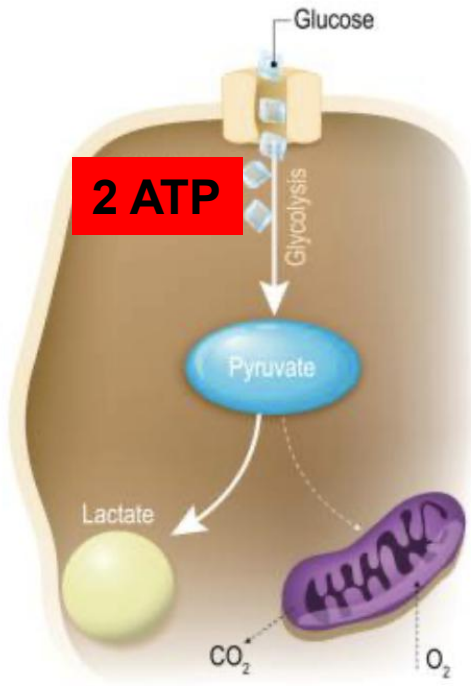
Slow-twitch fiber
(mitochondria)

Fast-twitch fiber
(glycolysis)

Mitochondria
(oxidative phosphorylation)



Glycolysis
(no mitochondria)

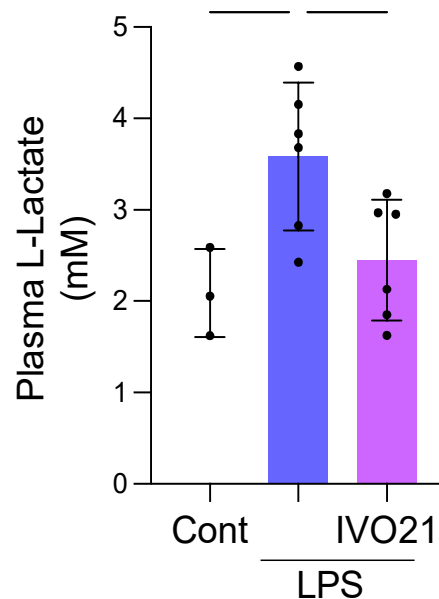


Lactic acid is inflammatory

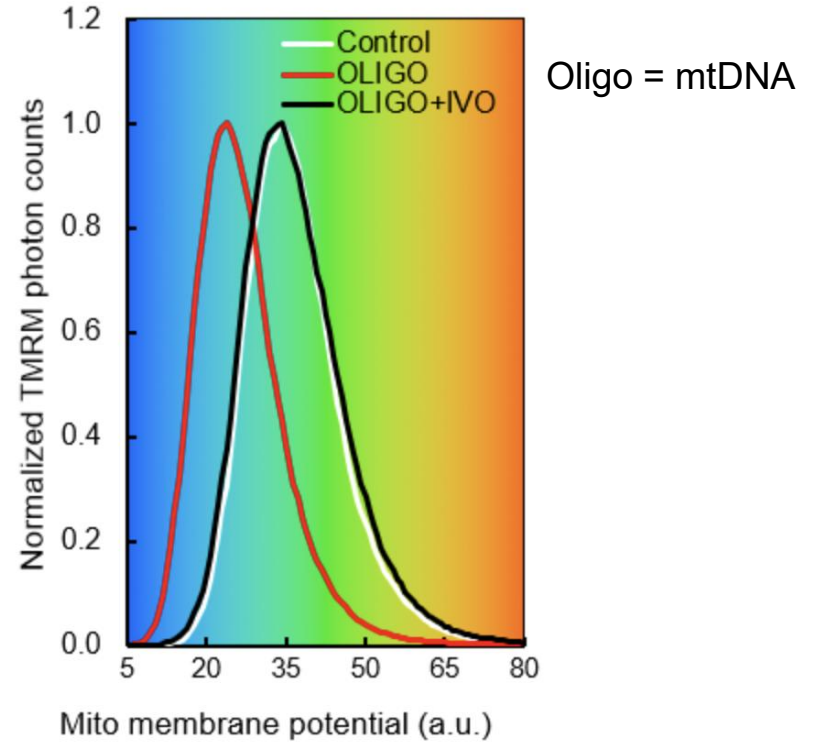
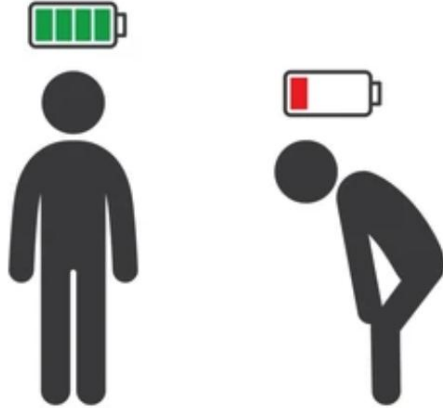
Lactic Acid Fermentation Is Required for NLRP3 Inflammasome Activation

Hsin-Chung Lin^{1,2}, Yu-Jen Chen^{3,4,5}, Yau-Huei Wei⁶, Hsin-An Lin⁷, Chien-Chou Chen⁷, Tze-Fan Liu⁸, Yi-Lin Hsieh⁹, Kuo-Yang Huang⁹, Kuan-Hung Lin¹⁰, Hsueh-Hsiao Wang⁸ and Lih-Chyang Chen^{8*}

¹ Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, ² Division of Clinical Pathology, Department of Pathology, Tri-Service General Hospital, Taipei, Taiwan, ³ Department of Radiation Oncology, MacKay Memorial Hospital, New Taipei City, Taiwan, ⁴ Department of Medical Research, MacKay Memorial Hospital, New Taipei City, Taiwan, ⁵ Department of Nursing, MacKay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan, ⁶ Center for Mitochondrial Medicine and Free Radical Research, Changhua Christian Hospital, Changhua, Taiwan, ⁷ Department of Medicine, Tri-Service General Hospital SongShan Branch, Taipei, Taiwan, ⁸ Department of Medicine, MacKay Medical College, New Taipei City, Taiwan, ⁹ Graduate Institute of Pathology and Parasitology, National Defense Medical Center, Taipei, Taiwan, ¹⁰ Institute of Biomedical Sciences, MacKay Medical College, New Taipei City, Taiwan



IVO-21 restores mitochondrial “charge”



IVO-21 increases lysosomal activity

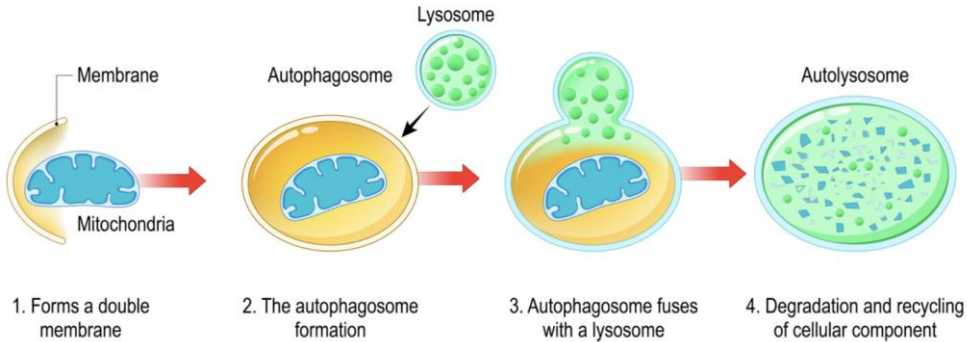
rapamycin



mTOR



autophagy

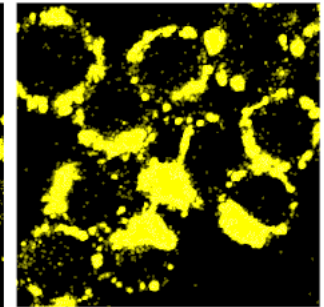
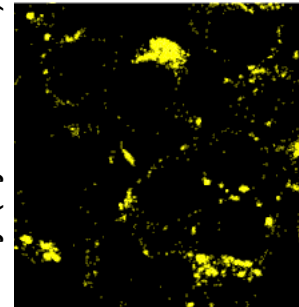
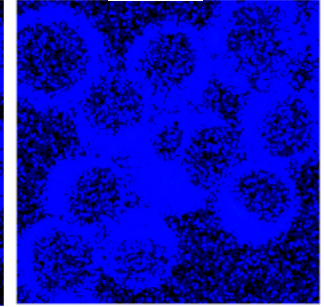
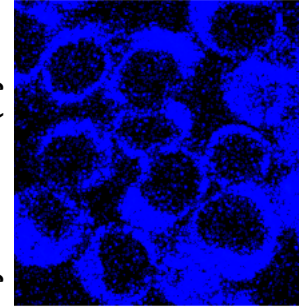


Lysosomal removal of damaged mitochondria

lysosome (LysoTracker)
acidity (LysoSensor)

(vehicle

(IVO h)



WASF3 disrupts mitochondrial respiration and may mediate exercise intolerance in myalgic encephalomyelitis/chronic fatigue syndrome

Ping-yuan Wang^{a,1}, Jin Ma^{a,1}, Young-Chae Kim ^a, Annie Y. Son^a, Abu Mohammad Syed ^a, Chengyu Liu ^b, Mateus P. Mori ^a, Rebecca D. Huffstutler^a, JoEllyn L. Stolinski^c, S. Lalith Talagala^c, Ju-Gyeong Kang^a, Brian T. Walitt^d, Avindra Nath ^d, and Paul M. Hwang ^{a,2}

Edited by Se-Jin Lee, University of Connecticut School of Medicine, Farmington, CT; received February 17, 2023; accepted June 27, 2023

August 14, 2023 | 120 (34) e2302738120 | <https://doi.org/10.1073/pnas.2302738120>

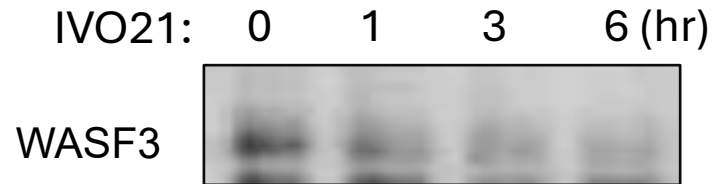
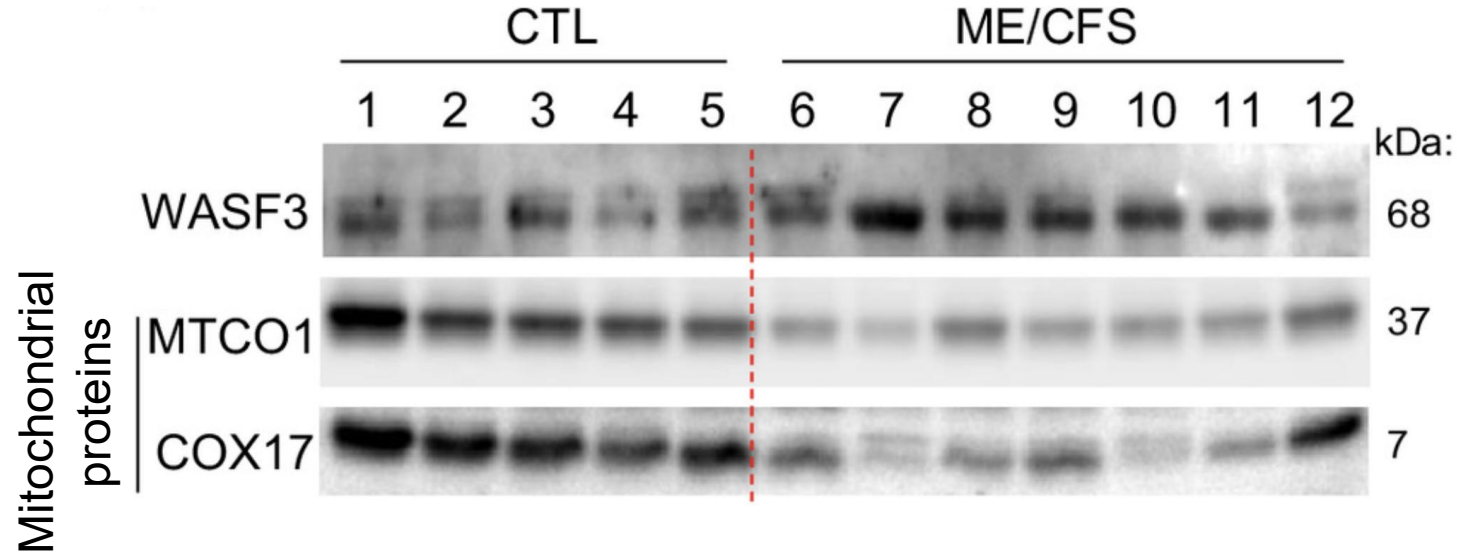
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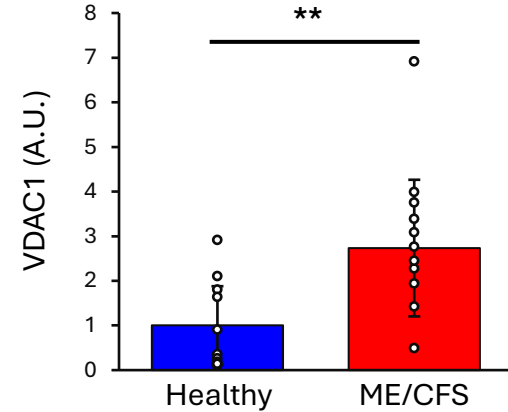
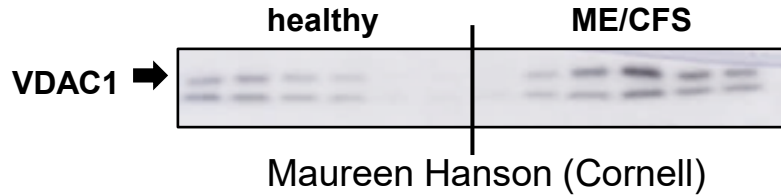
**Protein found that
disrupts energy levels
in ME/CFS**



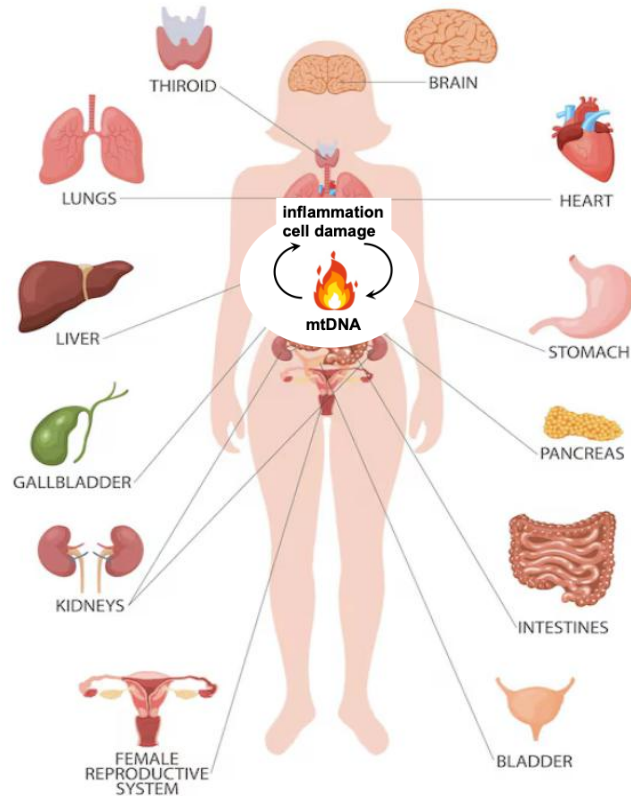
IVO-21 suppresses WASF3



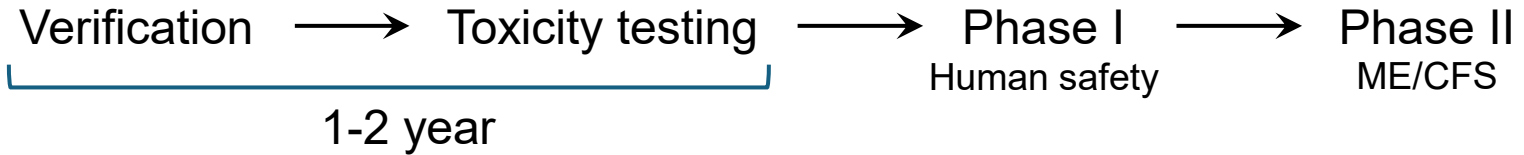
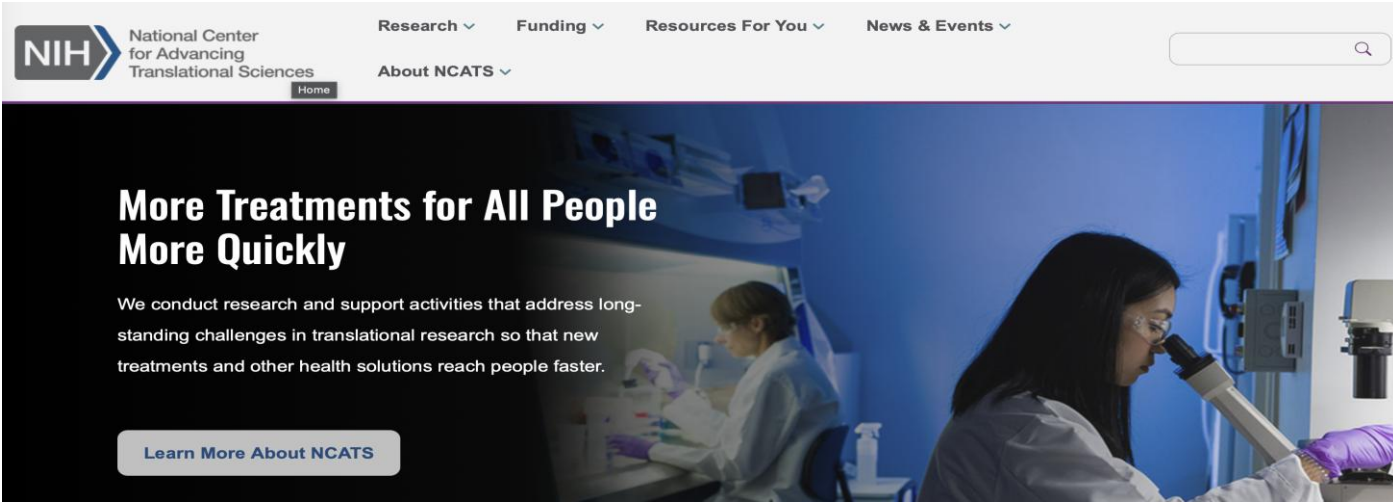
VDAC1 is elevated in ME/CFS



Clinical manifestations may depend on the organ in which the inflammatory cycle is established

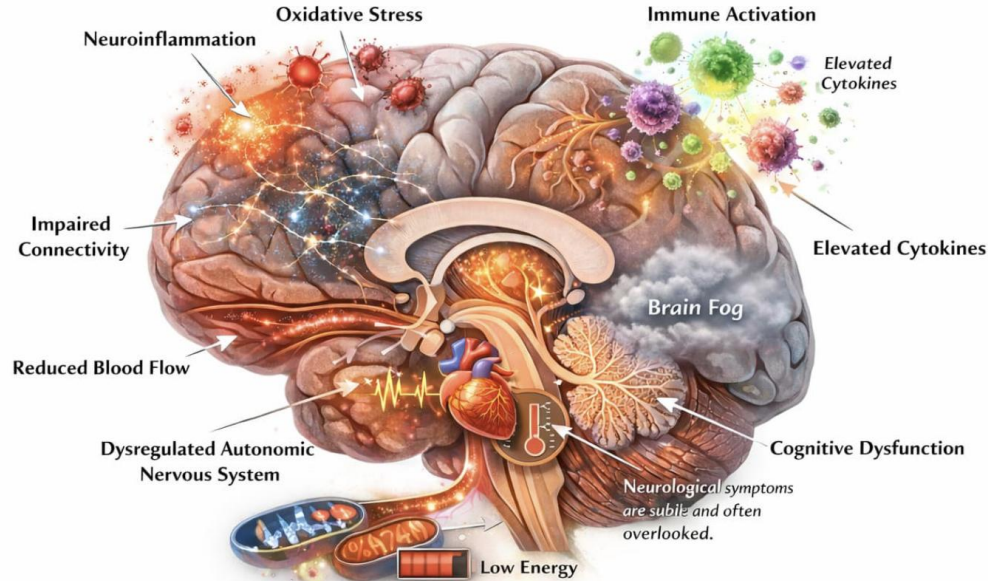


IVO-21 may not be effective if there is a hidden microbial reservoir



Why do we need animal models?

Chronic Fatigue Syndrome (ME/CFS)



Cannot recreate the complex long-term cell-cell interaction in a petri dish.

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Solve ME/CFS

