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Beyond the Symptom: The Biology of Fatigue

September 27 – 28, 2021

Immune Dysfunction in ME/CFS

Maureen Hanson

Cornell Center for Enervating Neuroimmune Disease

Disclaimer and Disclosures

Disclaimer

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure

This certifies that I, Maureen Hanson, have no financial relationship that is relevant to the subject matter of this presentation.

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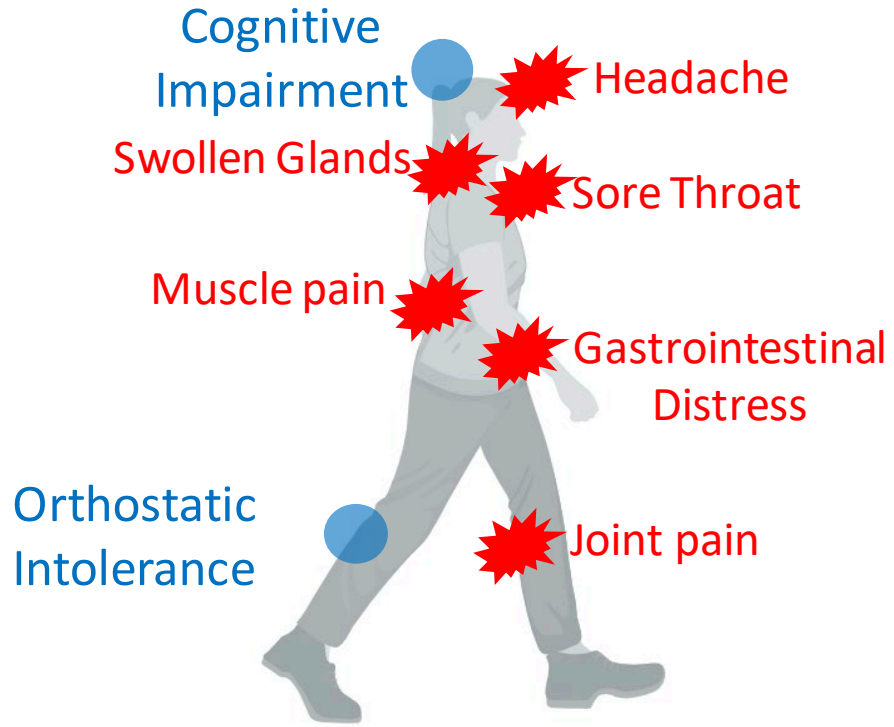
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): more symptoms than fatigue



4 or 5 of these symptoms diagnose ME/CFS

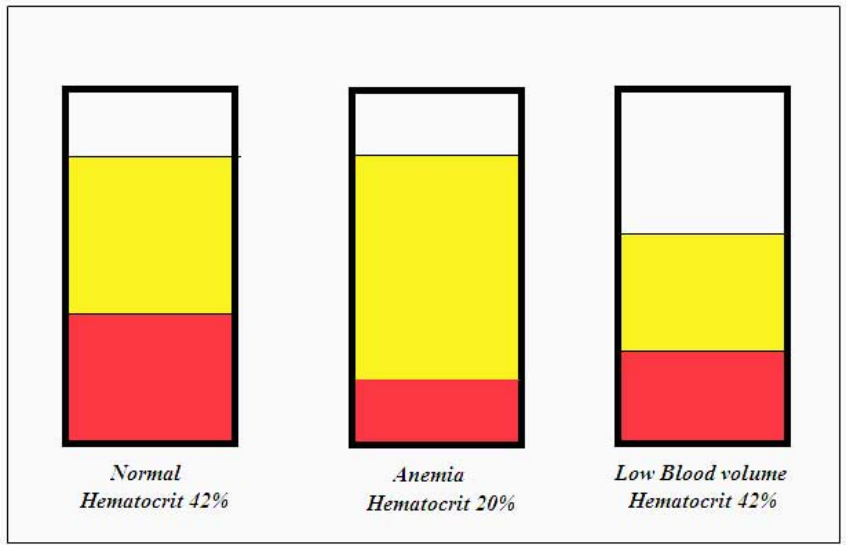
Common additional symptoms

Created with BioRender

How ME/CFS patients describe their illness

"I feel like I've been hit by a truck"

"I feel as if my body is trying to recover from a severe injury"



A significant percentage of ME/CFS patients have low blood volume

How ME/CFS patients describe their illness

“I feel drained of energy”

“I’m worn out, not like the fatigue from staying up late at night”

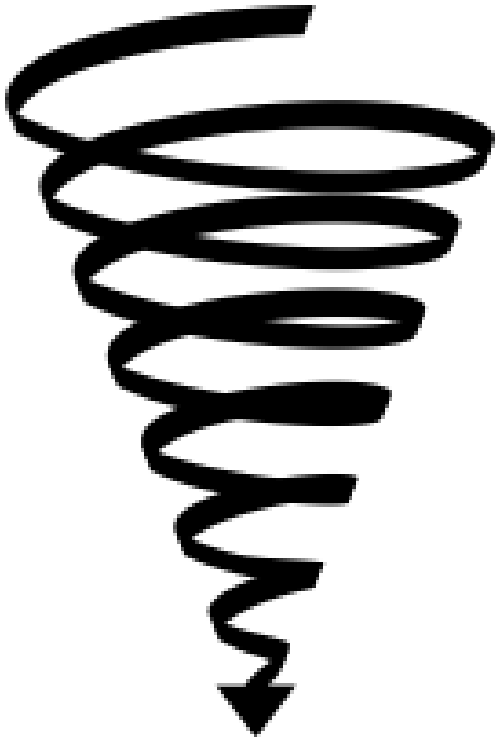
“I’m unable to recharge my battery by a good night’s sleep as I could before”

(Getty)

The fatigue of ME/CFS does not result from lack of psychological motivation

Post-exertional malaise is one of the most disabling symptoms

"I have the will to push through the fatigue to accomplish more but can't because of the penalty I'll pay afterward"



Push

⬇

Crash

Push

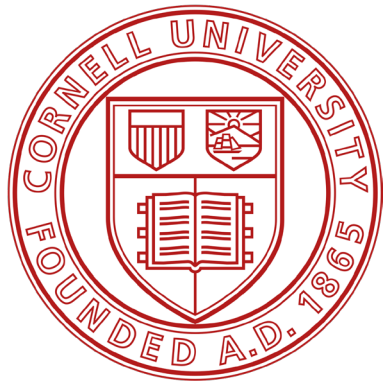
⬇

Crash

⬇

Permanent low level of function

Documented biological abnormalities in ME/CFS



ME/CFS Center

Altered response to exercise by cardiopulmonary exercise testing

Altered levels of plasma metabolites

Altered gut microbiome

Abnormal metabolism of immune cells

Reduced natural killer cell function

Altered levels of signaling proteins

Differences in gene expression in circulating immune cells

Changes in levels of molecules in the brain indicating increased oxidative stress or neuroinflammation

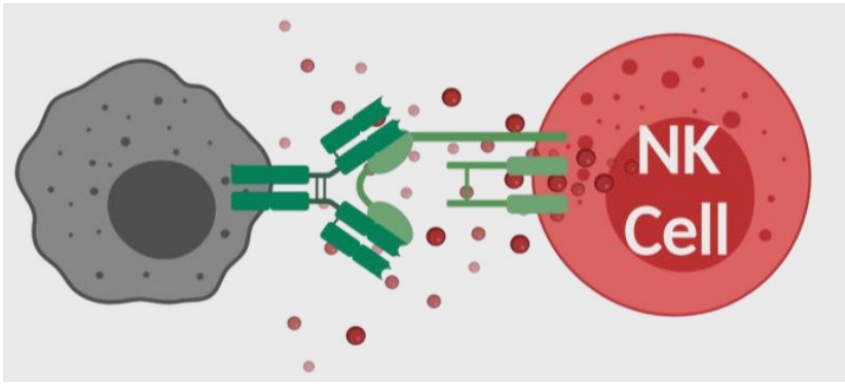
Abnormal natural killer cell function: repeatedly reproduced in ME/CFS

The Journal of Immunology

1987

Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome.

M Caligiuri, C Murray, D Buchwald, H Levine, P Cheney, D Peterson, A L Komaroff and J Ritz



Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/j.1365-2249.2005.02935.x

Chronic fatigue syndrome is associated with diminished intracellular perforin

2005

K. J. Maher,* N. G. Klimas*† and M. A. Fletcher*

*Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA, and †Department of Medicine, Veterans Administration Medical Center, Miami, FL, USA

OPEN ACCESS Freely available online PLoS one

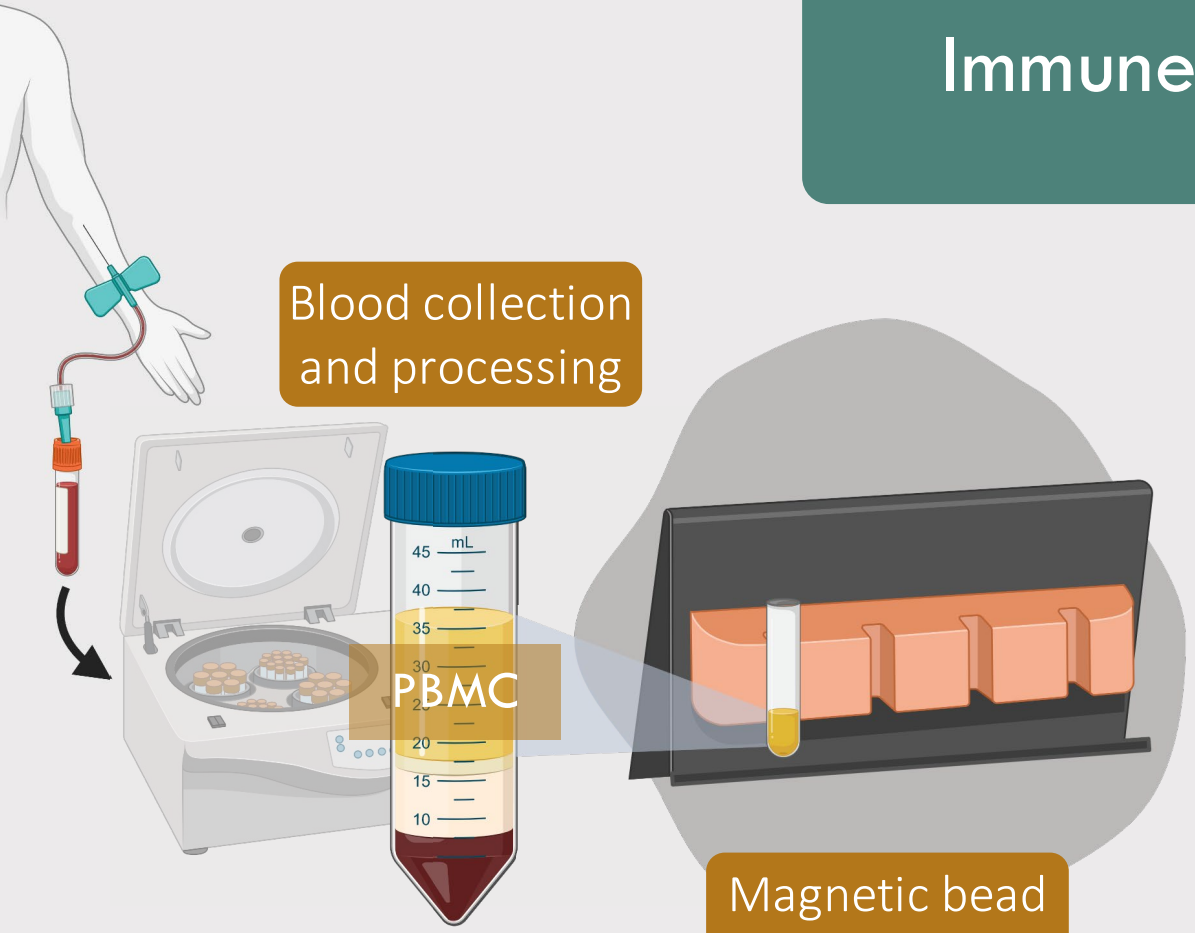
Biomarkers in Chronic Fatigue Syndrome: Evaluation of Natural Killer Cell Function and Dipeptidyl Peptidase IV/CD26

2010

Mary A. Fletcher[1,2,3*], Xiao R. Zeng[1,2], Kevin Maher[1], Silvina Levis[1,2], Barry Hurwitz[3], Michael Antoni[3], Gordon Broderick[4], Nancy G. Klimas[1,2,3]

Immune Metabolism

Blood collection and processing

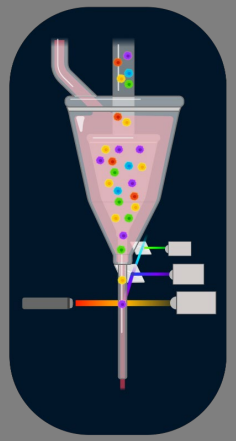


Magnetic bead isolation

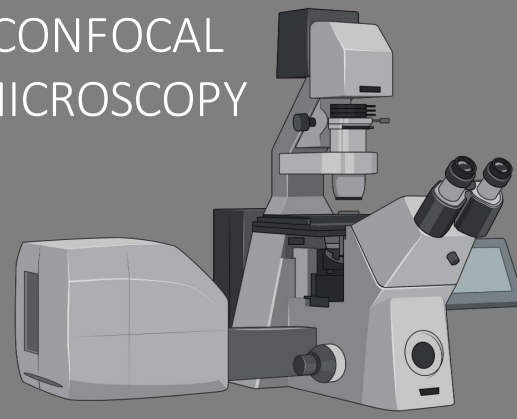
	Resting	Activated
CD4+ T cells		αCD3/ αCD28 & IL2
CD8+ T cells		
NK cells		IL15/ IL12

FLOW CYTOMETRY

Measure markers associated with metabolism and cell populations



CONFOCAL MICROSCOPY

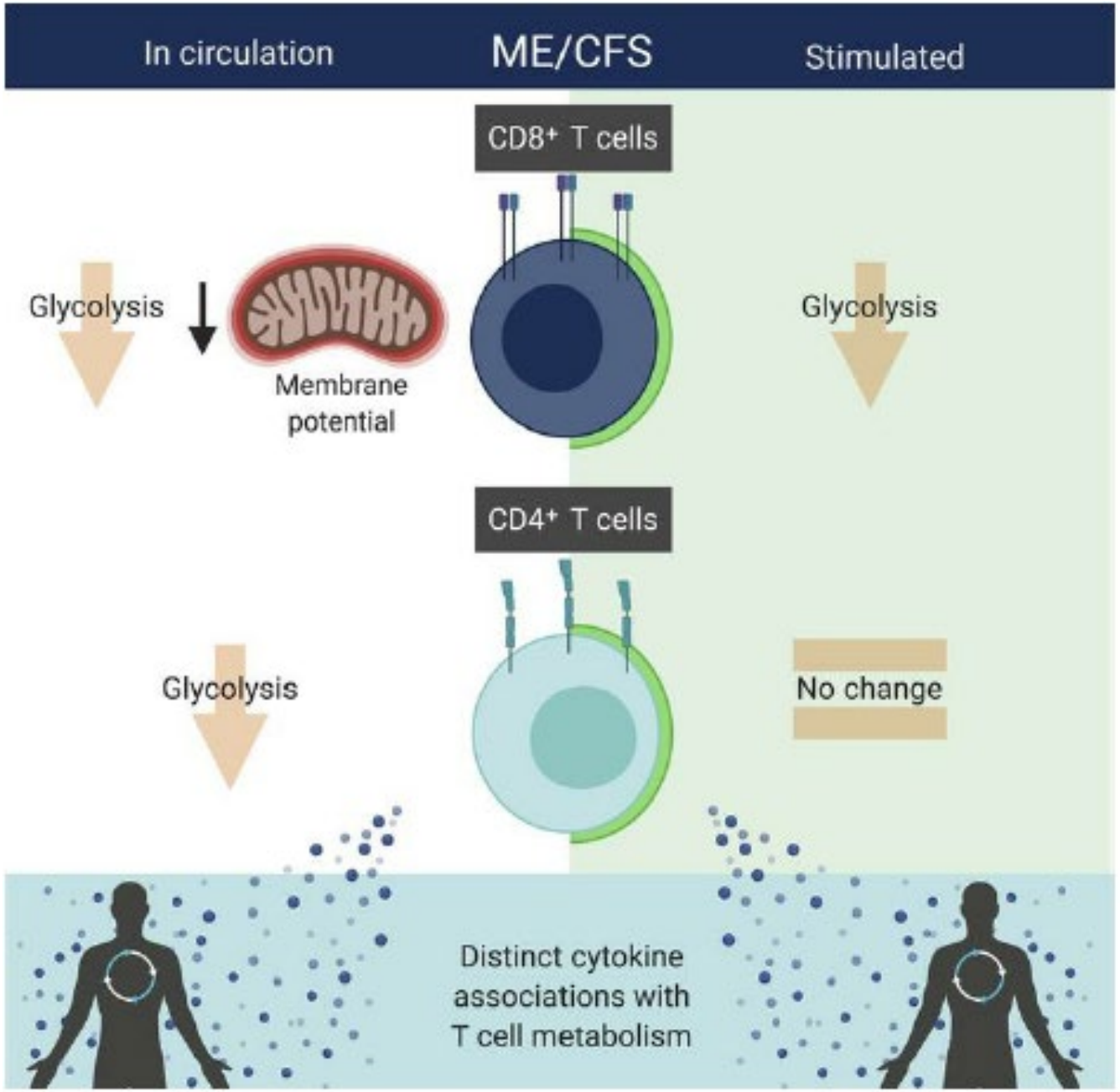


XFp SEAHORSE

Record live cell metabolic rates

Created by Jessica Maya with Biorender

Summary of prior study

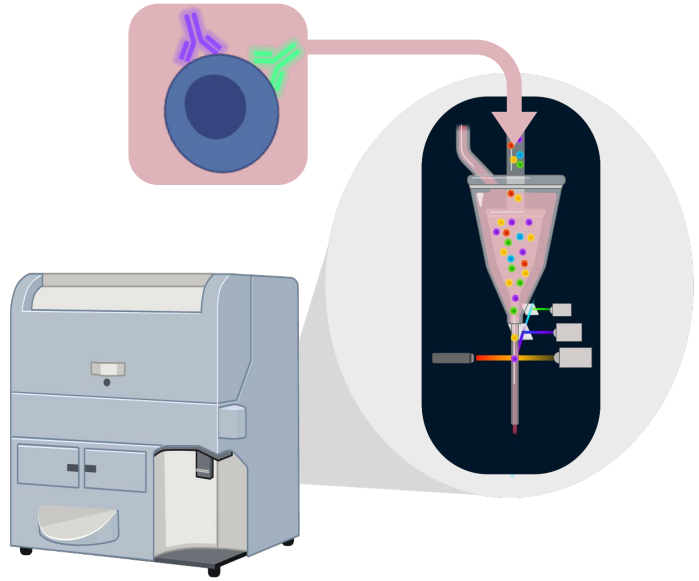


Mandarano AH, Maya J, Giloteaux L, Peterson DL, Maynard M, Gottschalk CG, Hanson MR. 2020 Myalgic encephalomyelitis/chronic fatigue syndrome patients exhibit altered T cell metabolism and cytokine associations. J Clinical Investigation 130(3): 1491-1505. PMID: 31830003

Do immune cells in ME/CFS vs controls differ in fatty acid oxidation?

CD36
Long chain fatty acid transporter located on the cell membrane

CPT1a
Long chain fatty acid transporter located on the mitochondria



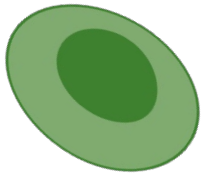
Flow cytometry to determine the level of the transporters

XFp SEAHORSE

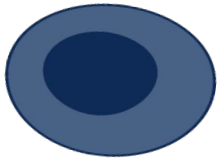
Record live cell metabolic rates

Use etomoxir, an inhibitor of fatty acid oxidation, to determine its effect on respiration

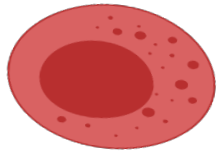
Current data about fatty acid oxidation in immune cells

CD4+ T cells 

Increased use of fatty acid oxidation in circulating cells from ME/CFS

CD8+ T cells 

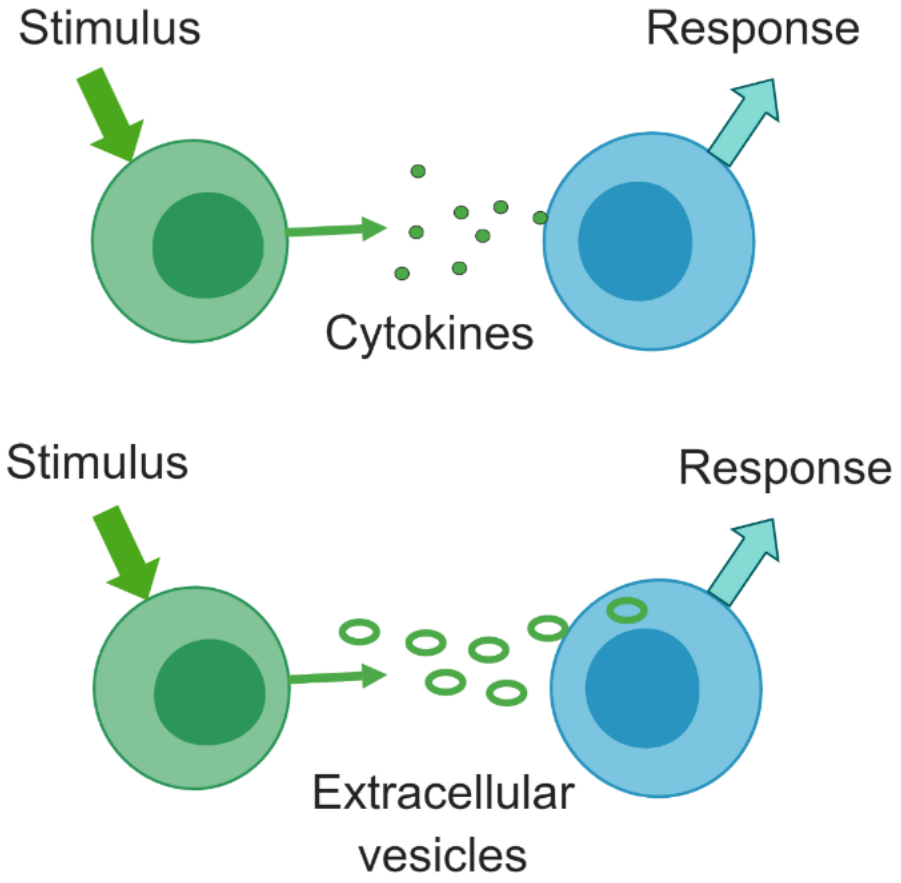
Slightly higher use of fatty acid oxidation in circulating cells from ME/CFS

NK cells 

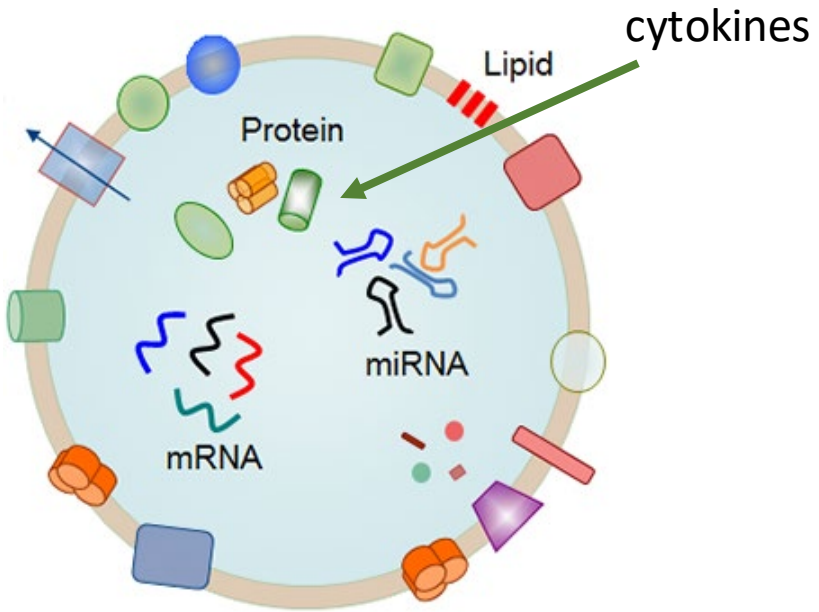
After activation: in ME/CFS cells, higher mitochondrial fatty acid transporter CPT1a abundance and lower CD36 cell membrane fatty acid transporter

Jessica Maya

Does cytokine signaling differ in ME/CFS?

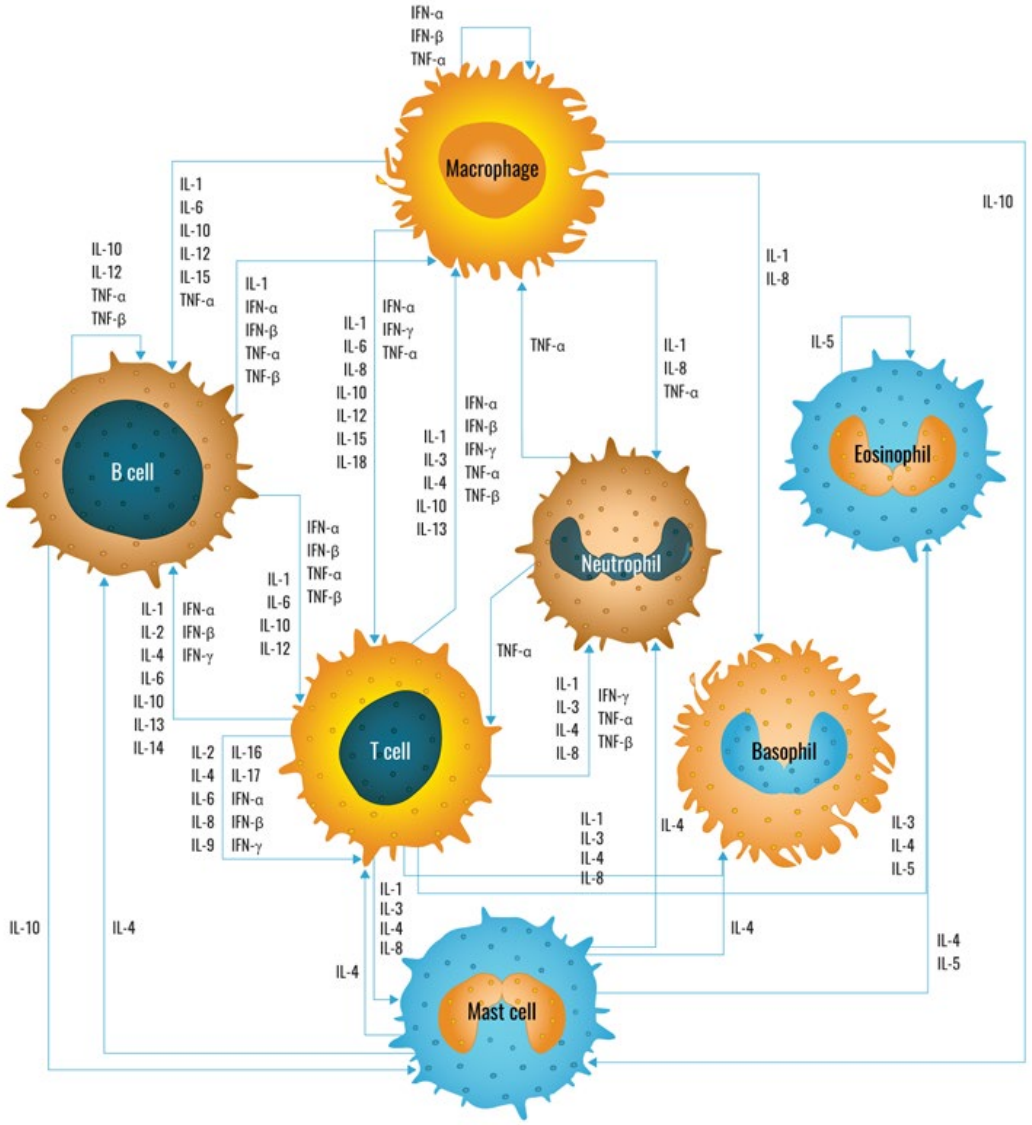


Cytokines can be secreted from cells or packaged in extracellular vesicles (EVs)



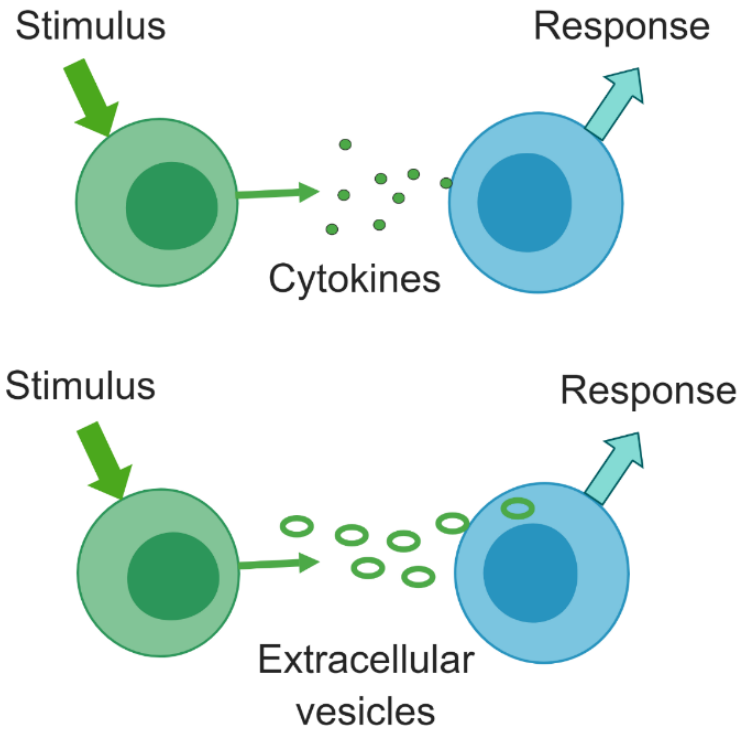
Extracellular vesicle

Cytokine networks



Particular molecules are released by one type of cell, taken up by other cells, which are then stimulated to release other cytokines

How does exercise affect the networks of cytokines in plasma and extracellular vesicles?



Post-exertional malaise

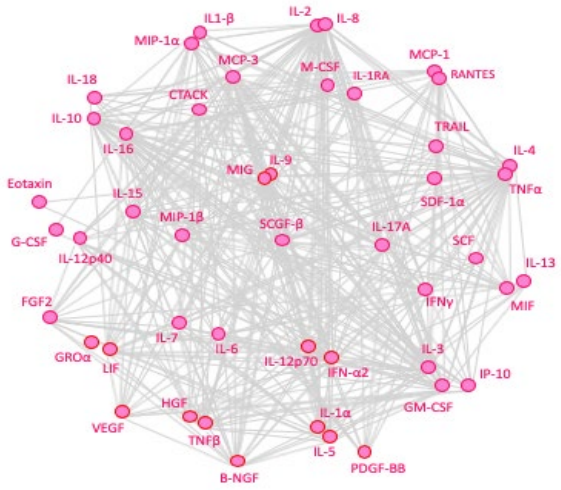
Ludovic Giloteaux
Postdoc Associate

Cytokine-cytokine correlations in plasma

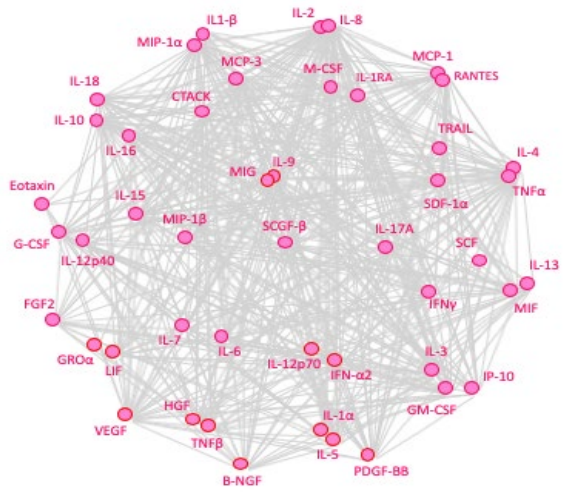
positive correlations

negative correlations

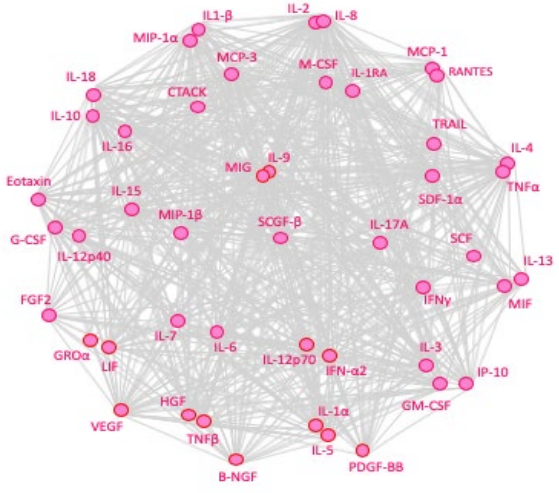
Controls preDay1



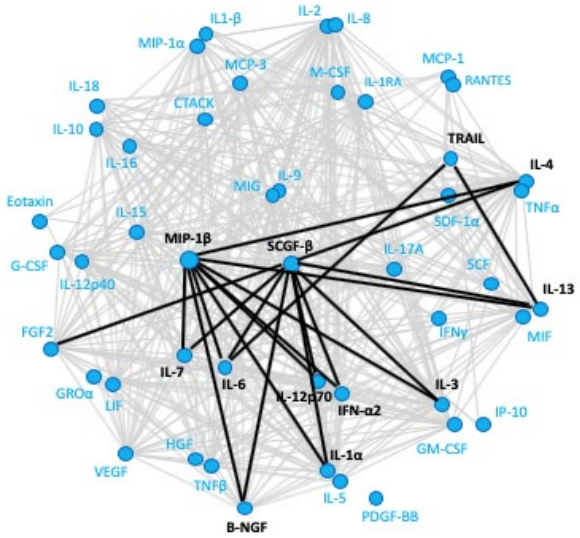
Controls postDay1



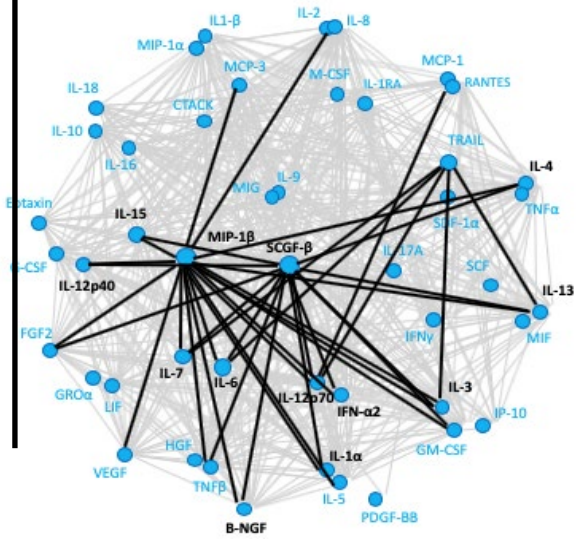
Controls preDay2



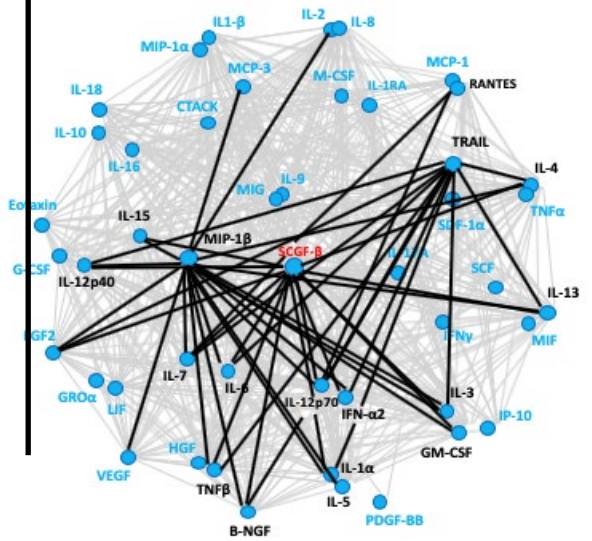
ME/CFS preDay1



ME/CFS postDay1



ME/CFS preDay2

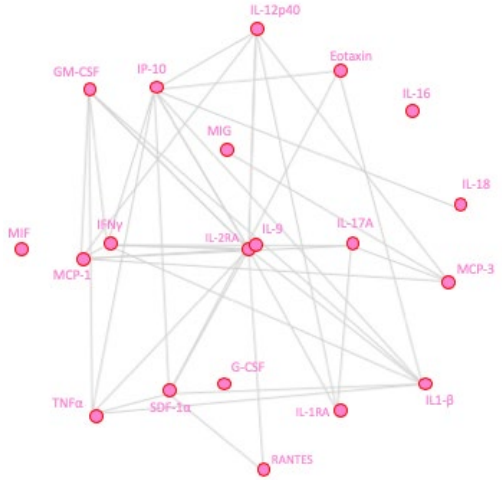


Cytokine-cytokine correlations in extracellular vesicles

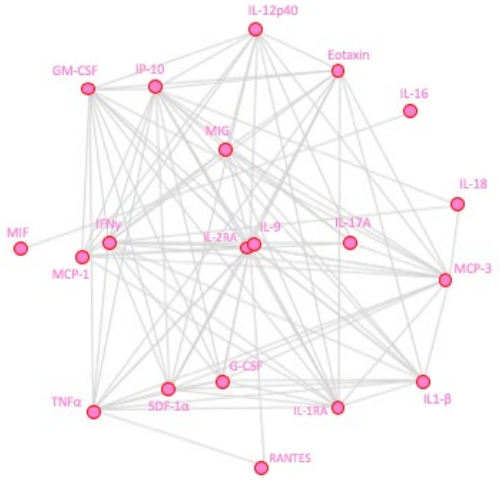
positive correlations

negative correlations

Controls preDay1



Controls postDay1



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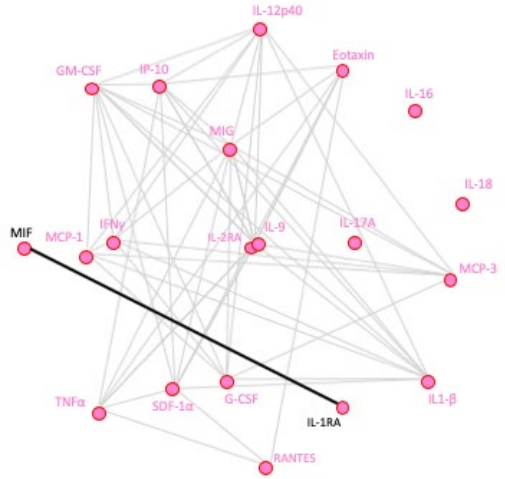
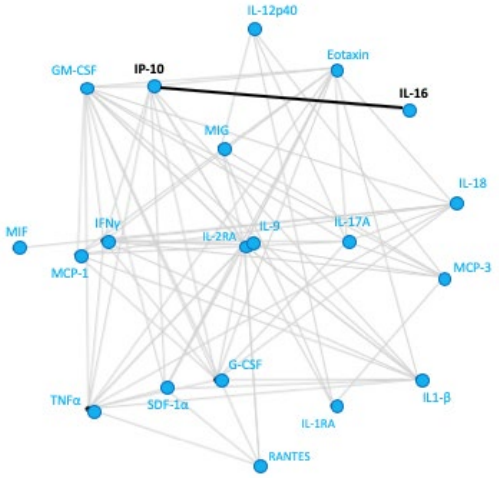
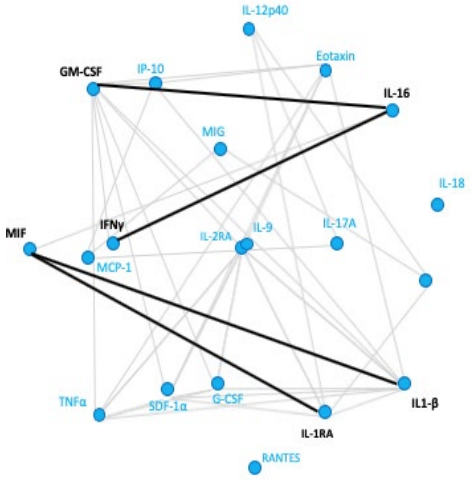


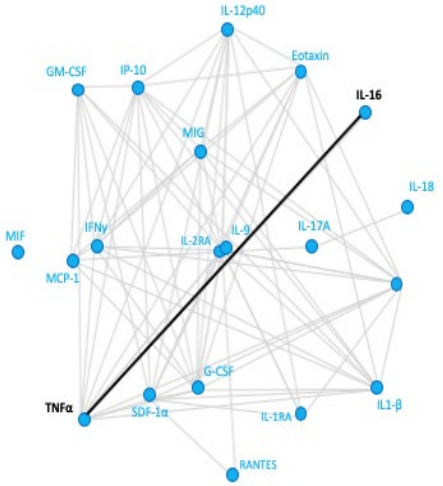
ME/CFS preDay1



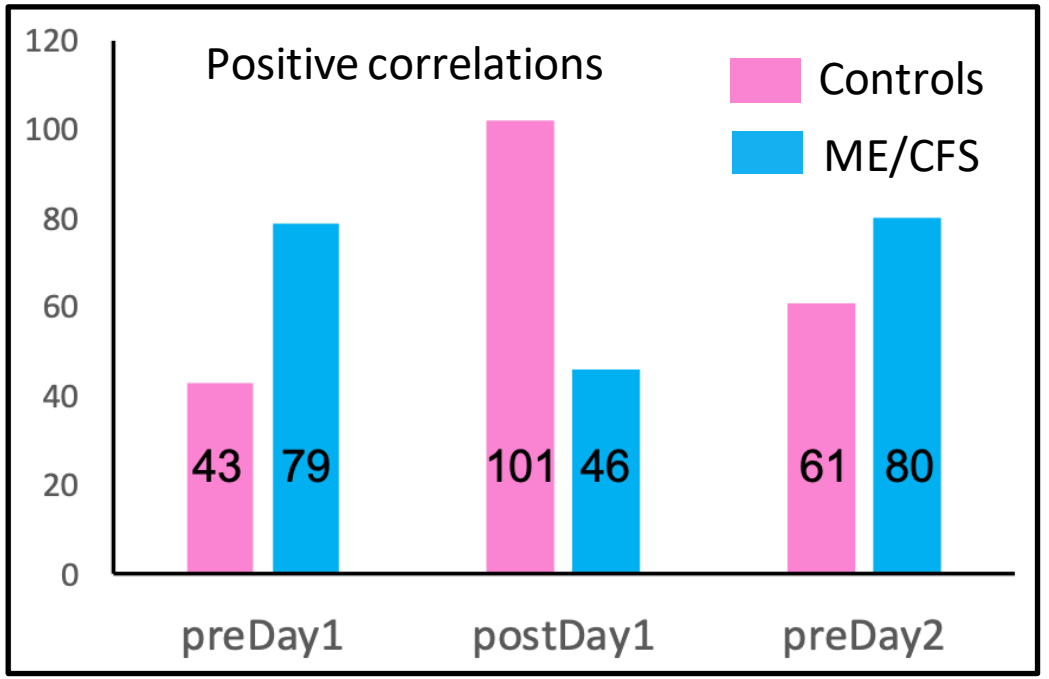
ME/CFS postDay1



ME/CFS preDay2



Cytokine networks differ between ME/CFS and controls at baseline and between the two post-exercise time points measured



Take-home messages

Metabolism of T and NK cells differs between ME/CFS and control subjects

Cytokine networks differ between ME/CFS and controls subjects at baseline and following an exercise challenge

Take-home questions

How is altered immune metabolism and signaling related to the fatigue and other symptoms of ME/CFS?

Can immune modulating drugs be used to restore normal functioning of the immune system?

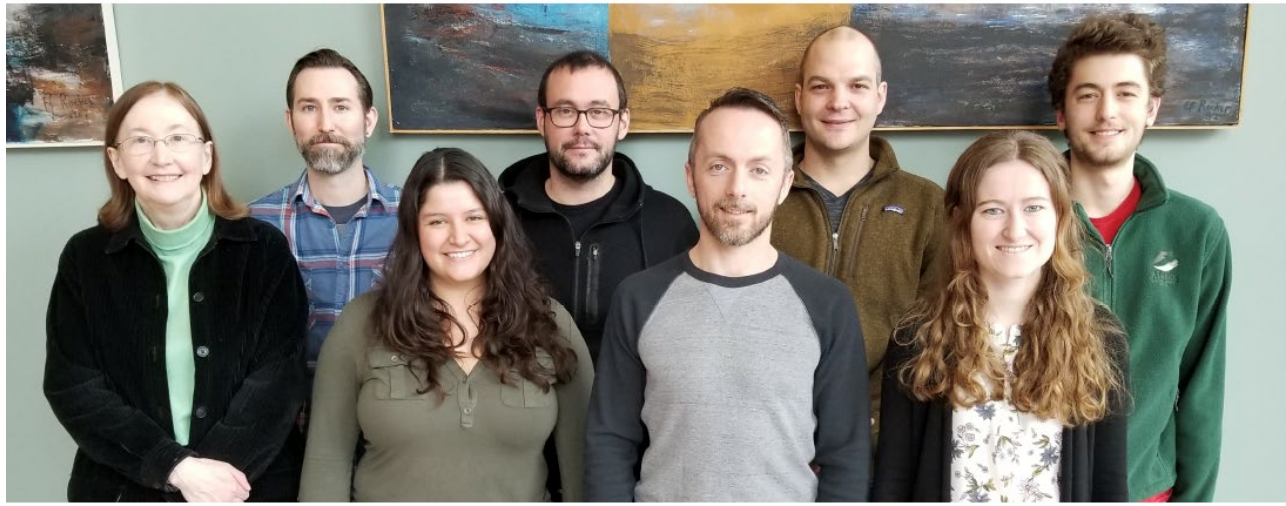
What underlying abnormality results in the altered immune signaling?

Cornell University

Center for Enervating NeuroImmune Disease

https://neuroimmune.cornell.edu

Carl Franconi Ludovic Giloteaux Adam O'Neal Ivan Falsztyn



Maureen Hanson Jessica Maya Arnaud Germain Alexandra Mandarano

Additional Cornell NIH Center researchers

Betsy Keller
Geoffrey Moore
Susan Levine
John Chia
Staci Stevens
Jared Stevens
Andrew Grimson
Dikoma Shungu
Xiangling Mao

Simmaron Research
Scientifically Redefining ME/CFS

Daniel Peterson
Gunnar Gottschalk
Marco Maynard

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