



CDC Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Stakeholder Engagement and Communication (MECFS-SEC) Webinar/Conference Call

September 23, 2020



AGENDA

- Welcome – Christine Pearson
- CDC Program Overview – Dr. Beth Unger
- Guest Speaker – Dr. Maureen Hanson
- Questions and Answers

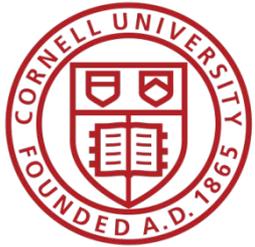
Federal Relay

Event ID: 4537697

For closed captioning, please visit

<https://www.captionedtext.com/client/event.aspx?EventID=4537637&CustomerID=321>

The findings and conclusions in these presentations are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



Immune Dysfunction in ME/CFS

Maureen Hanson

Department of Molecular Biology and Genetics

Cornell Center for Enervating Neuroimmune Disease



The Reality of ME/CFS



Few people with the illness are able to work full-time

At least 25% are housebound or bedbound

The most severely ill victims cannot speak, eat, nor tolerate light and sound

Prognosis is poor; fewer than 5% of adults recover most of their prior function

No FDA-approved drug for treatment

A majority of patients indicate onset after a viral-like illness

Pendergrast T, Brown A, Sunnquist M, et al. Housebound versus nonhousebound patients with myalgic encephalomyelitis and chronic fatigue syndrome. *Chronic Illness*. 2016;12:292-307.

<https://www.nap.edu/catalog/19012/beyond-myalgic-encephalomyelitis-chronic-fatigue-syndrome-redefining-an-illness>

Outbreaks of ME/CFS implicate one or more infectious agents

Elk Grove, California	1990	
Lyndonville, NY (between Rochester and Buffalo)	1985	
Incline Village, Nevada	1984	
Chapel Hill, NC (NC Orchestra)	1984	
West Otago, New Zealand	1982-1984	
Mercy San Juan Hospital, Sacramento, California	1975	
Lackland Air Force Base, Texas	1970	
Royal Free Hospital, England	1955	
Adelaide, Australia	1949-1951	
Frohburg Hospital , St. Gallen, Switzerland	1937	Not a complete list: see large compilation in <i>The Clinical and Scientific Basis of Myalgic Encephalomyelitis - Chronic Fatigue Syndrome</i> , 1992 Byron Hyde et al., ed.
Los Angeles County Hospital	1934	

What could cause continued symptoms following an acute infection?

Chronic infection

either by inciting organism

or by loss of control of known chronic infections (e.g. EBV) or

endogenous retroviruses

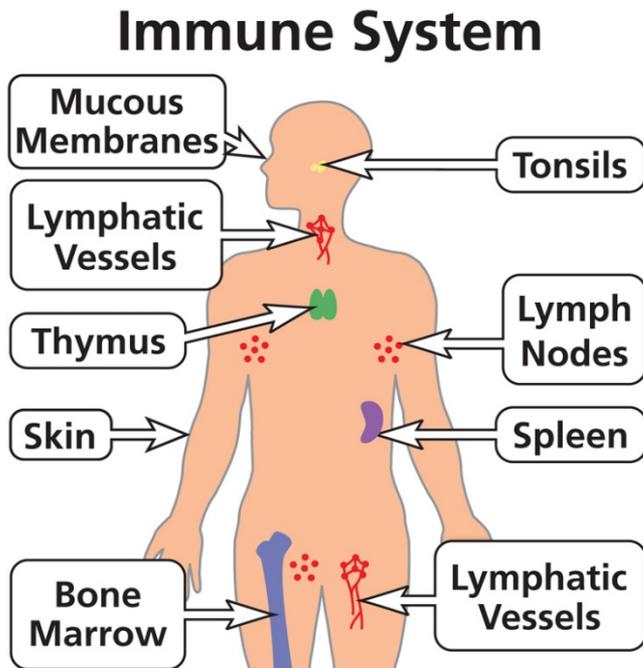
Damage from the acute infection

Epigenetic alterations in response to the infection

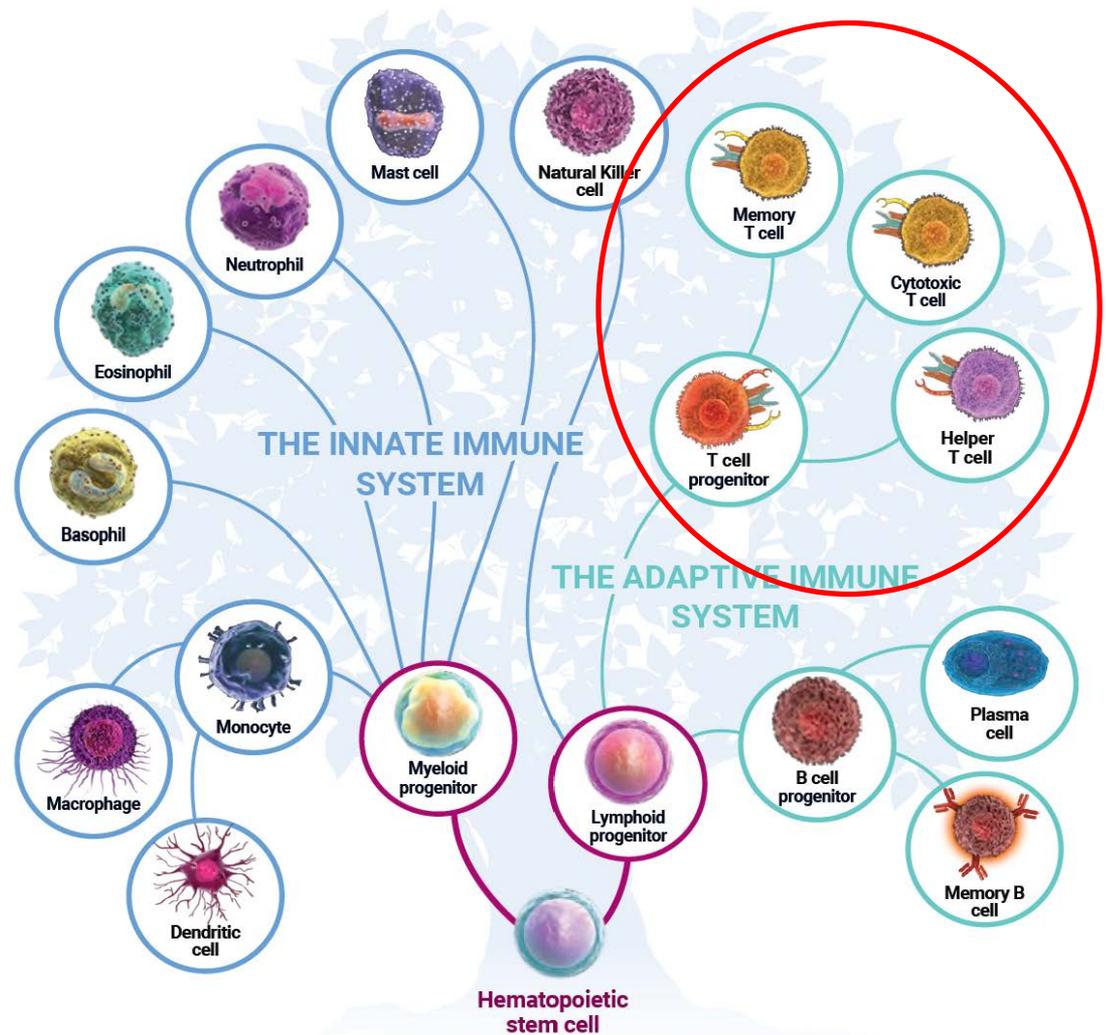
Autoimmunity

Disrupted microbiomes

The Immune System

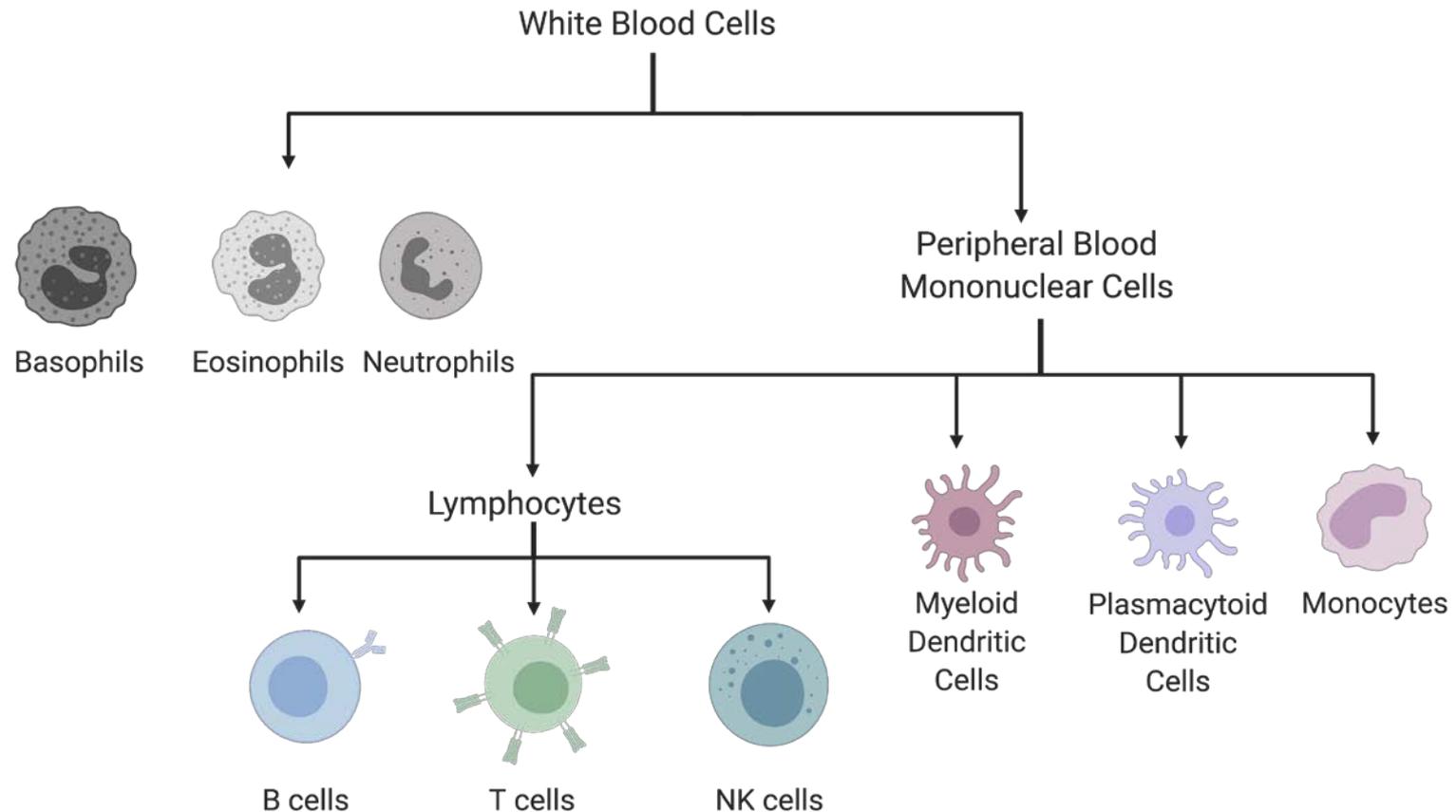


NIH.gov

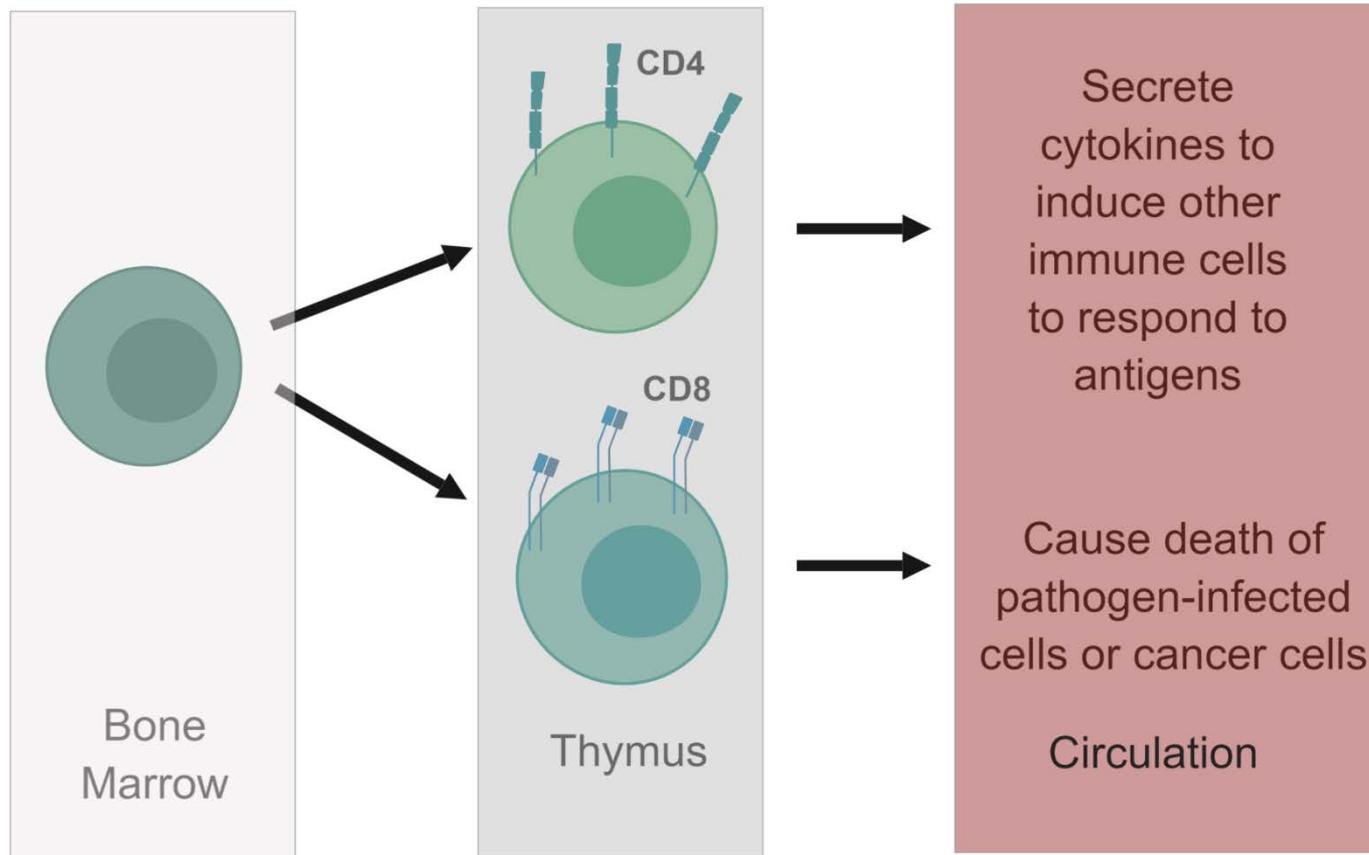


<https://lab-a-porter.com/>

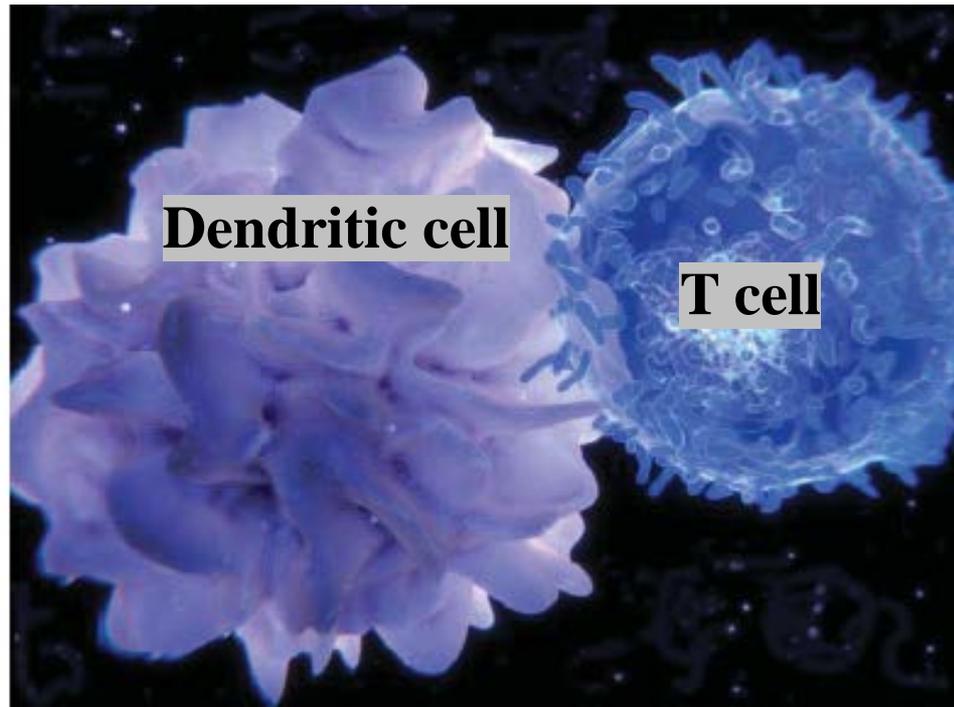
Analyzing specific cell types in peripheral blood will reveal features that cannot be detected when mixed cell populations are assayed



T cells are key elements of the immune system



T cells become activated when they interact with a dendritic cell that informs them of the presence of a foreign antigen

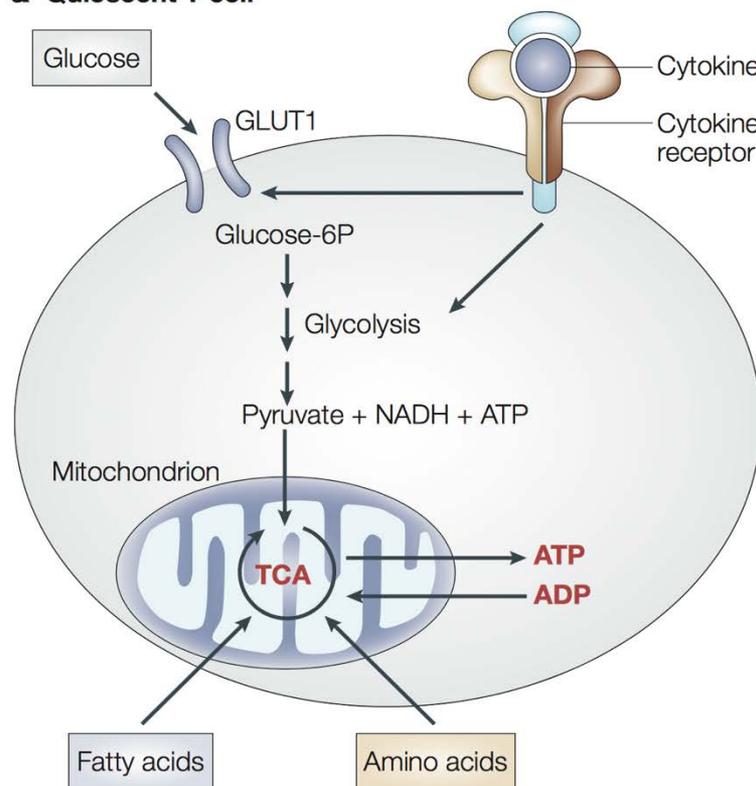


Dendritic cell
presenting an antigen
to a T cell

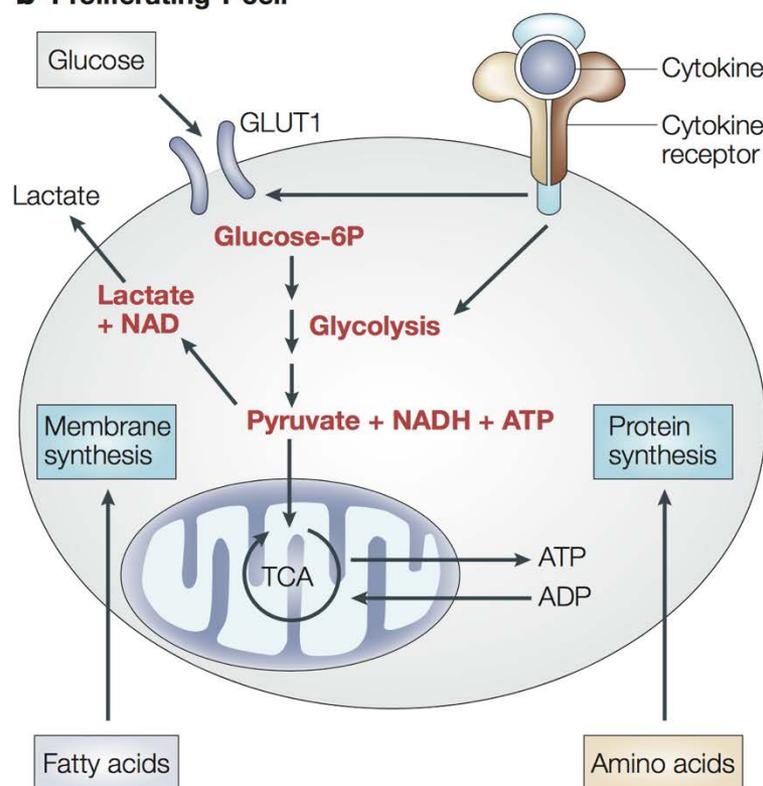
T cell made in
the Thymus

T cells use various types of energy sources to maintain themselves and to respond to activation signals

a Quiescent T cell



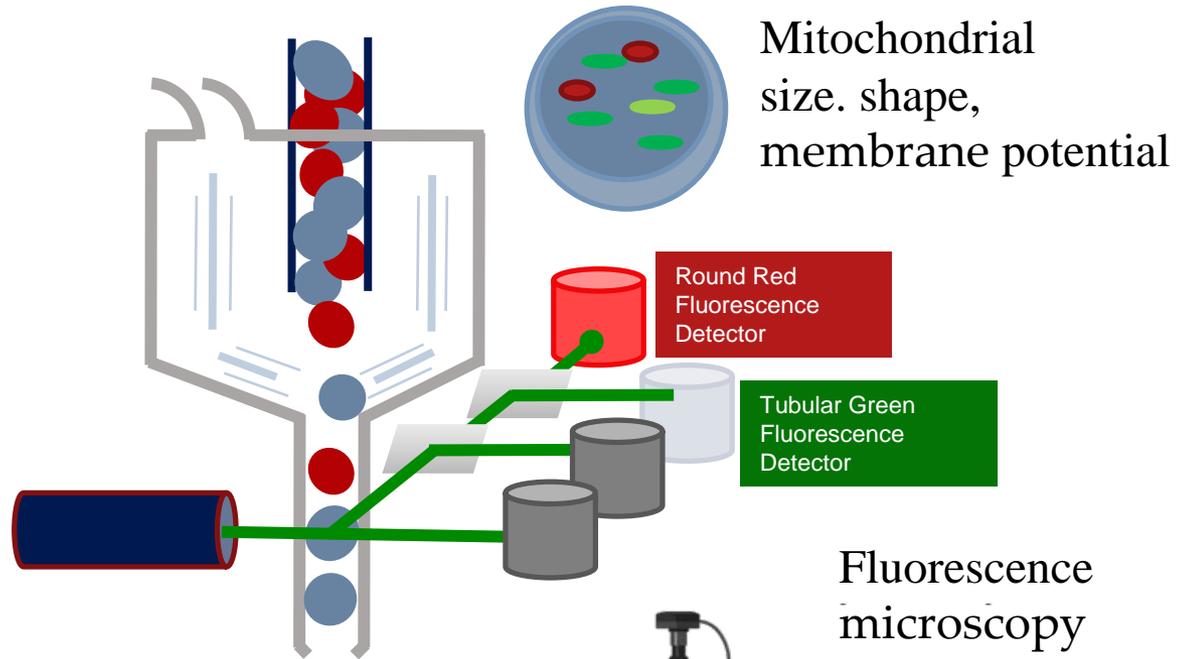
b Proliferating T cell



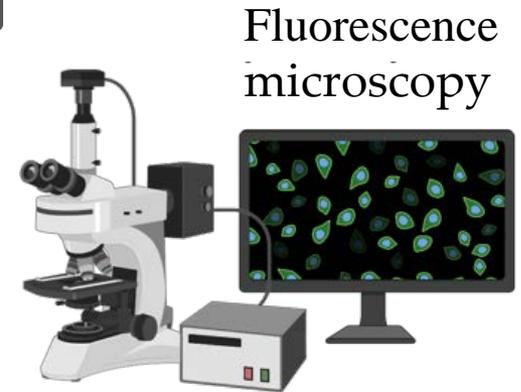
The energetic functioning of T cells can be examined by measures of metabolic pathways and mitochondrial characteristics



Agilent Seahorse assays
to measure activity of:
Oxidative phosphorylation
Glycolysis
Fatty acid oxidation



Flow cytometry

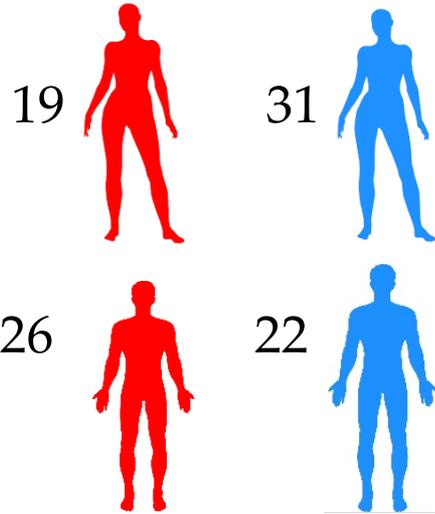


Fluorescence microscopy

Patient population for T cell study

45 Controls

53 ME/CFS

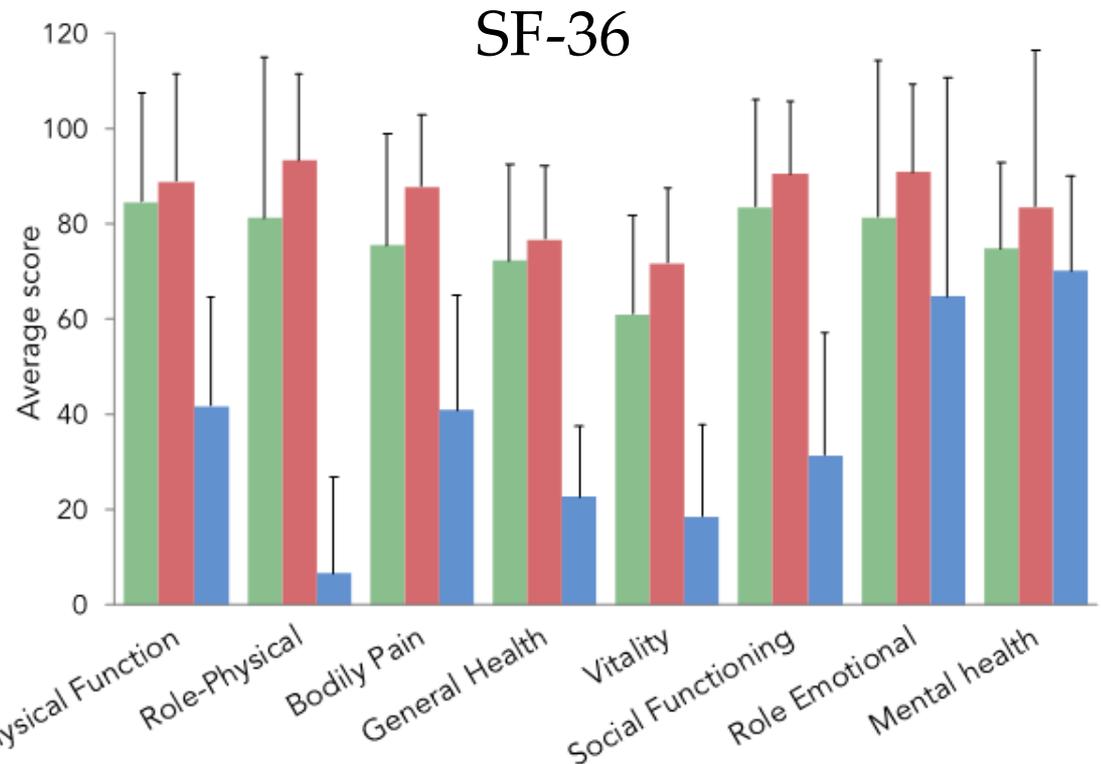


Illness duration
21.7 ± 12 yrs

Simmaron Research

Scientifically Redefining ME/CFS

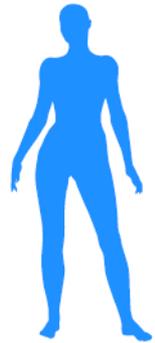
Daniel Peterson, M.D.
Gunnar Gottschalk
Marco Maynard
Jineet Patel
Incline Village, Nevada



■ US norms
 ■ Controls
 ■ ME/CFS

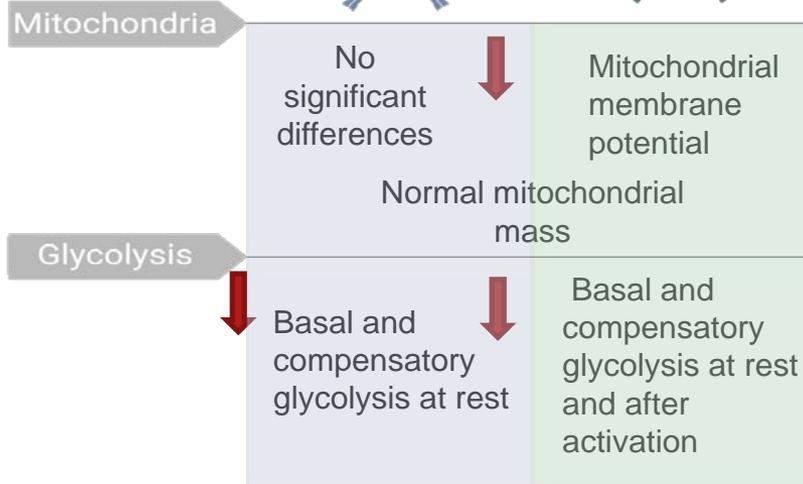
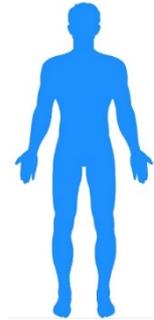
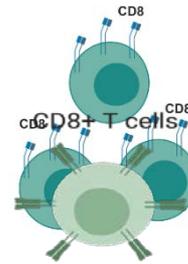
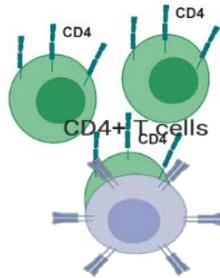
Maximum Disability No Disability
 0 100

Dysfunction of CD4+ and CD8+ T Cells in ME/CFS



CD4+ T cells

CD8+ T cells



More in:

Harvard OMF Symposium

[https://www.youtube.com/watch?time_continue=1&v=QAdZNU6](https://www.youtube.com/watch?time_continue=1&v=QAdZNU6D7Gs)

[D7Gs](https://www.youtube.com/watch?time_continue=1&v=QAdZNU6D7Gs)

Videos from

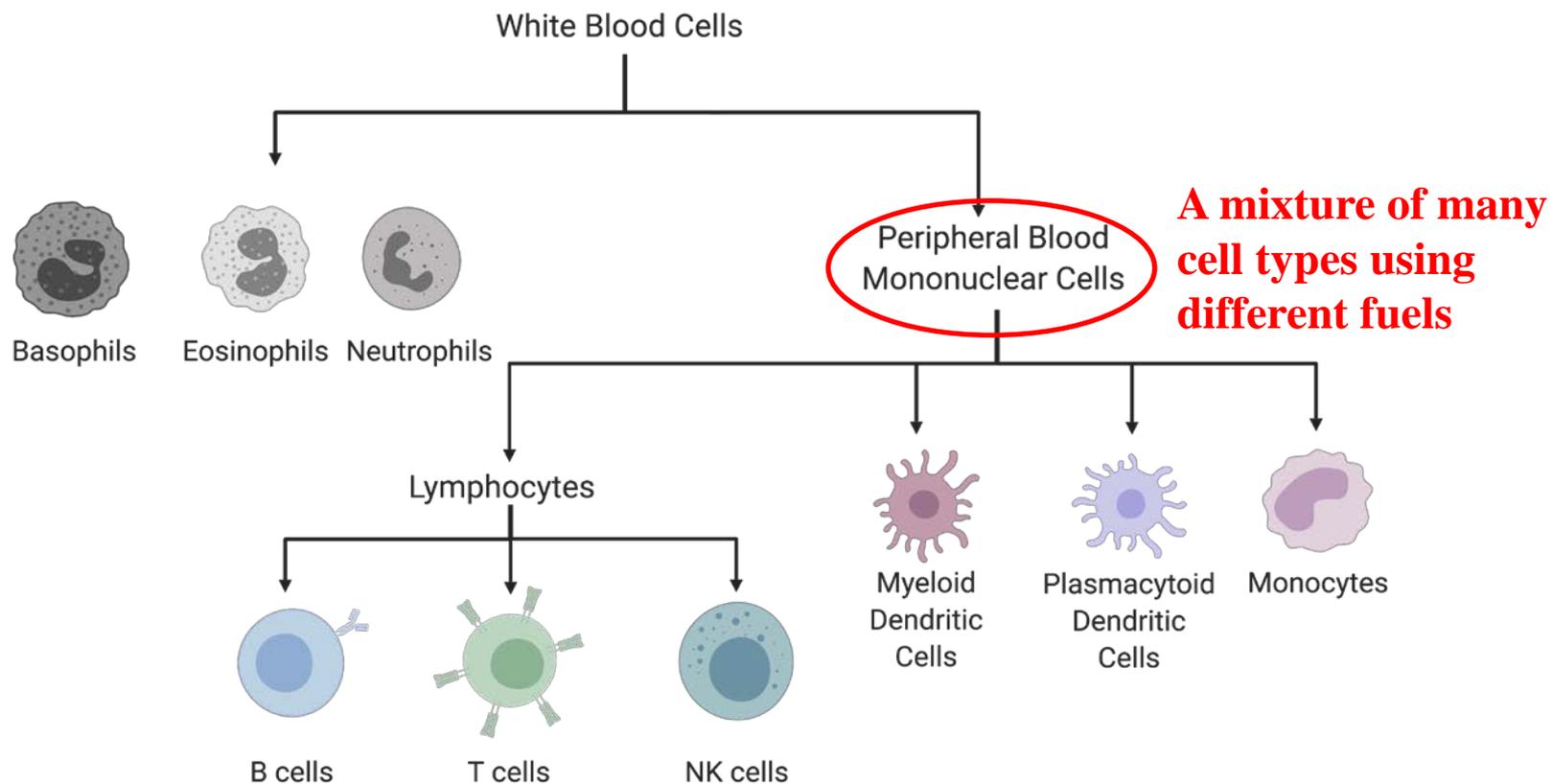
InvestinME Conference and the April NIH Conference at

<https://neuroimmune.cornell.edu/news/>

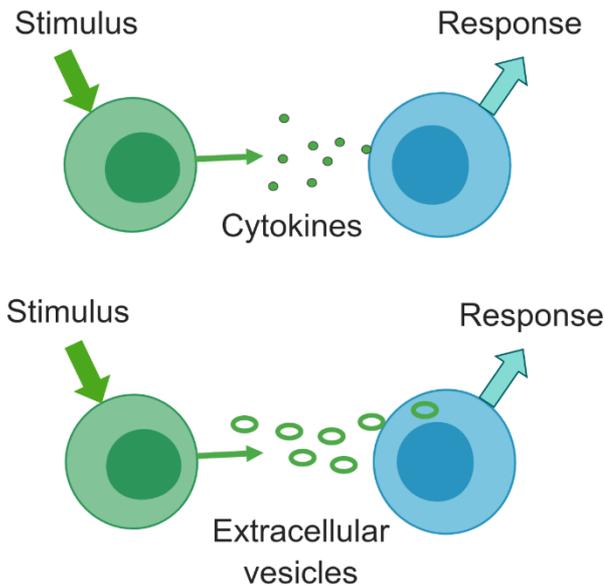
Myalgic encephalomyelitis/chronic fatigue syndrome patients exhibit altered T cell metabolism and cytokine associations

Alexandra H. Mandarano,¹ Jessica Maya,¹ Ludovic Giloteaux,¹ Daniel L. Peterson,² Marco Maynard,³ C. Gunnar Gottschalk,³ and Maureen R. Hanson¹

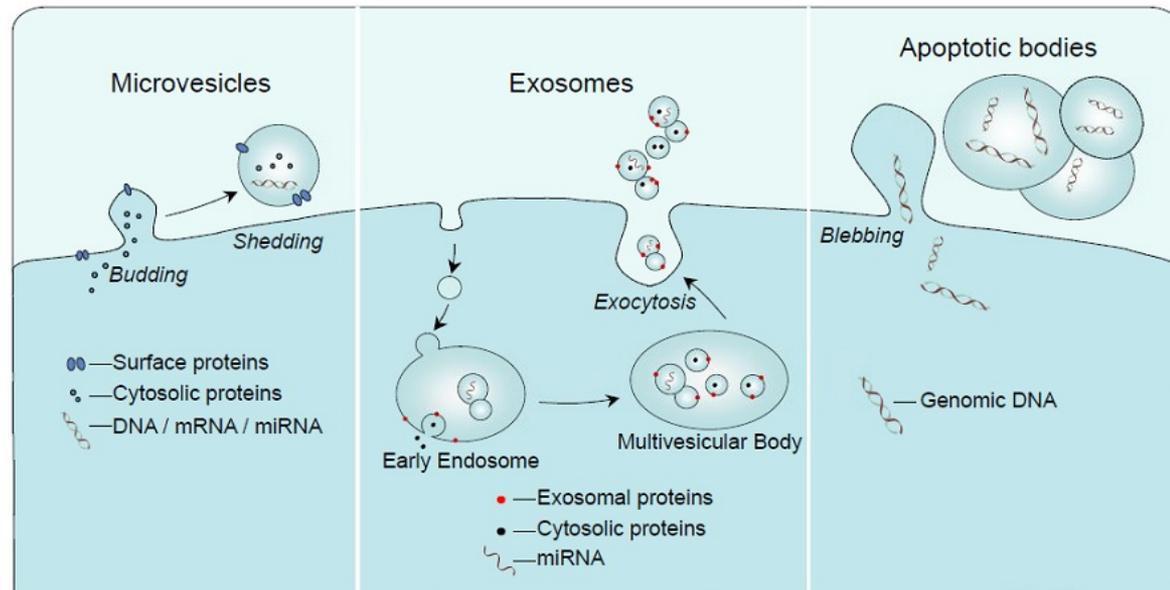
Assays of metabolism of immune cells tell about the functioning of the immune system: not necessarily applicable to other tissues and organs in the body



Immune cells also communicate through both release and uptake of both plasma cytokines and extracellular vesicles

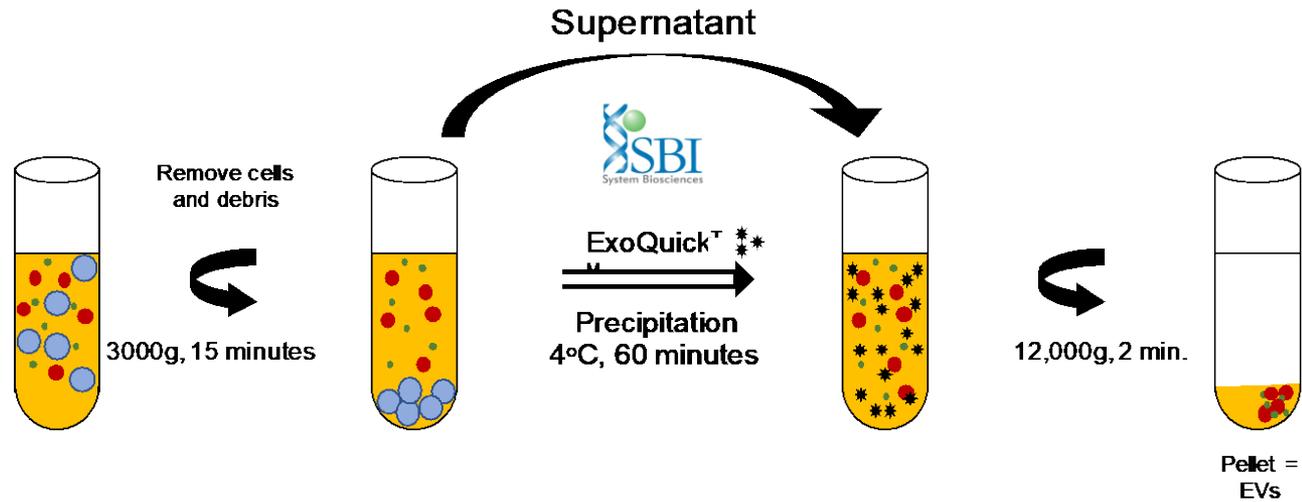


All three types of vesicles were isolated together by a plasma precipitation method



EV PRECIPITATION

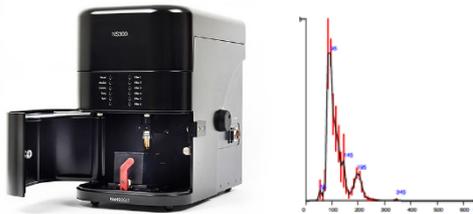
Purification and characterization of EVs from plasma



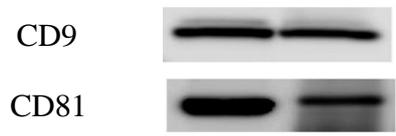
Nanoparticle Tracking Analysis

Immunoblot

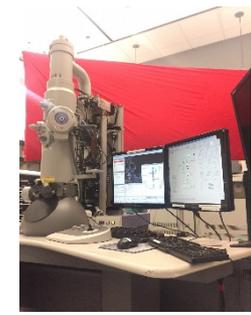
Transmission Electron Microscopy



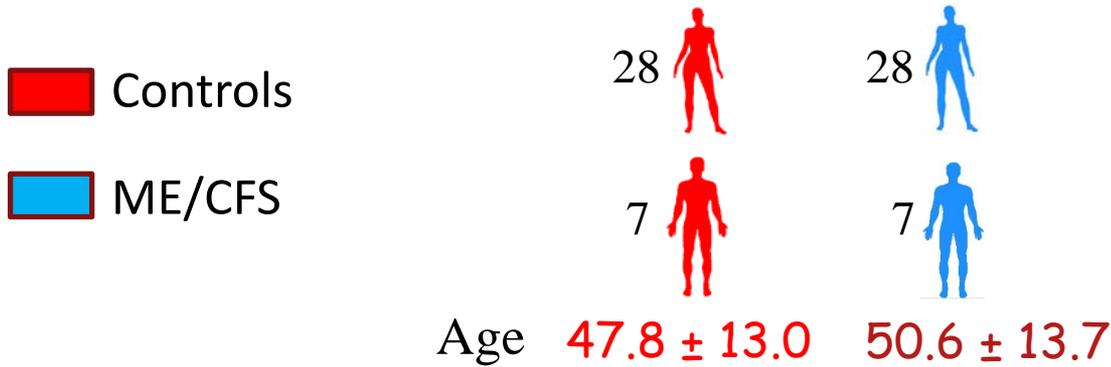
Size and number



Protein markers

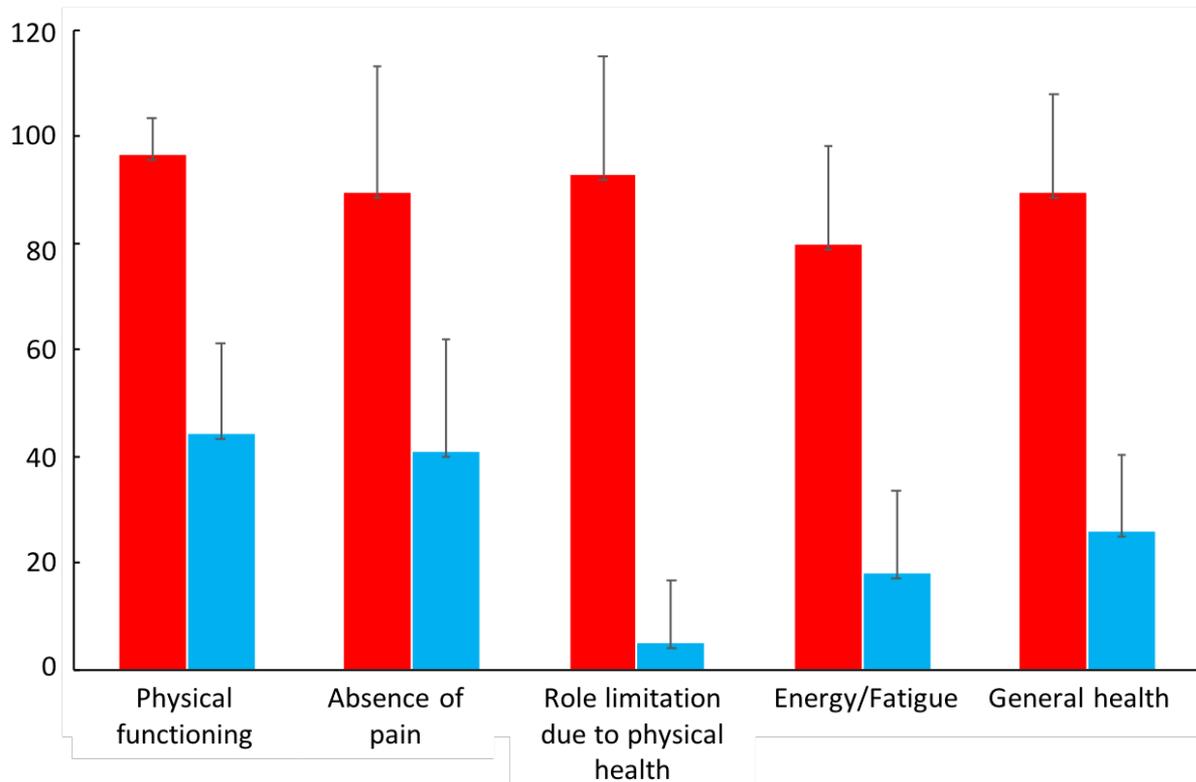


Study Population for Extracellular Vesicle Study



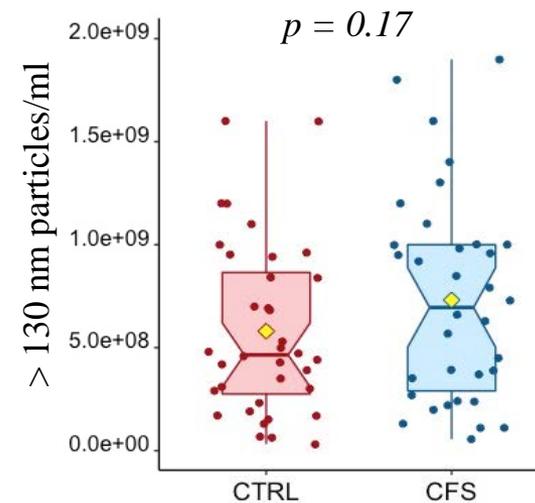
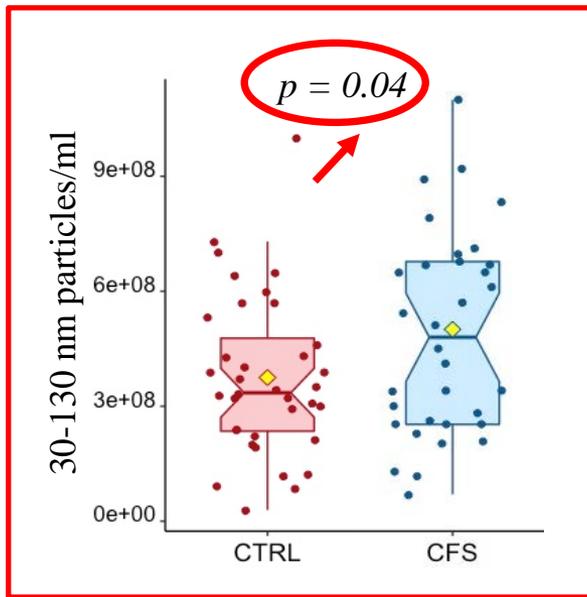
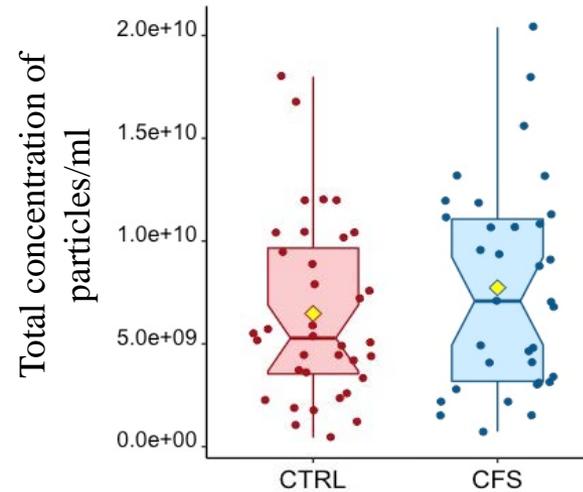
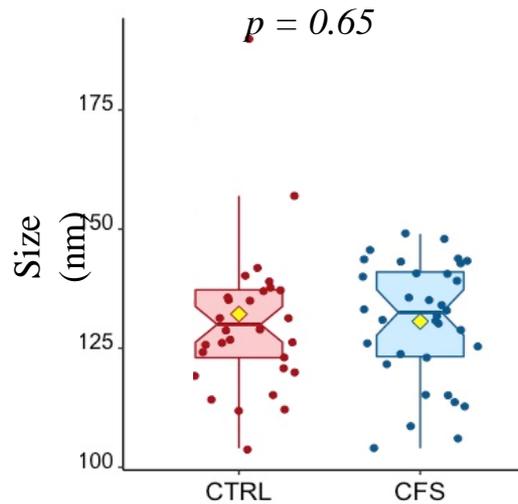
Manhattan, NY

Subjects recruited by
Susan Levine, M.D.



SF-36

Concentration of smallest particles (exosomes) is higher in ME/CFS subjects



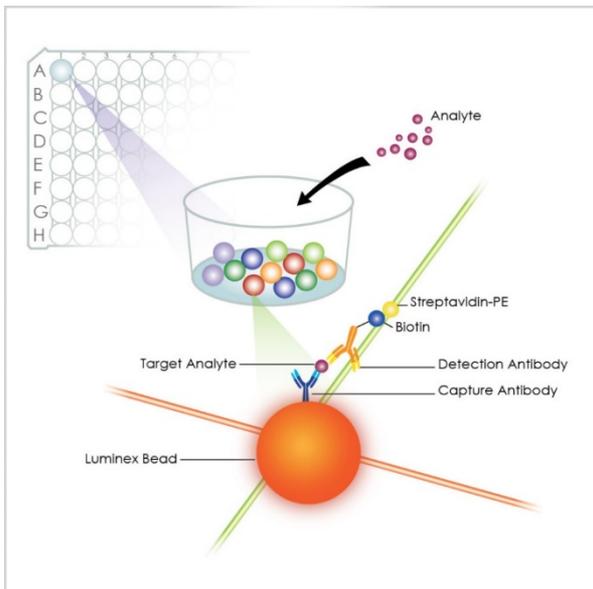
Samples from 38 subjects were analyzed for cytokines EVs and whole plasma

19  ME/CFS and 19  CTRLS in both EVs and whole plasma



Luminex
Magpix

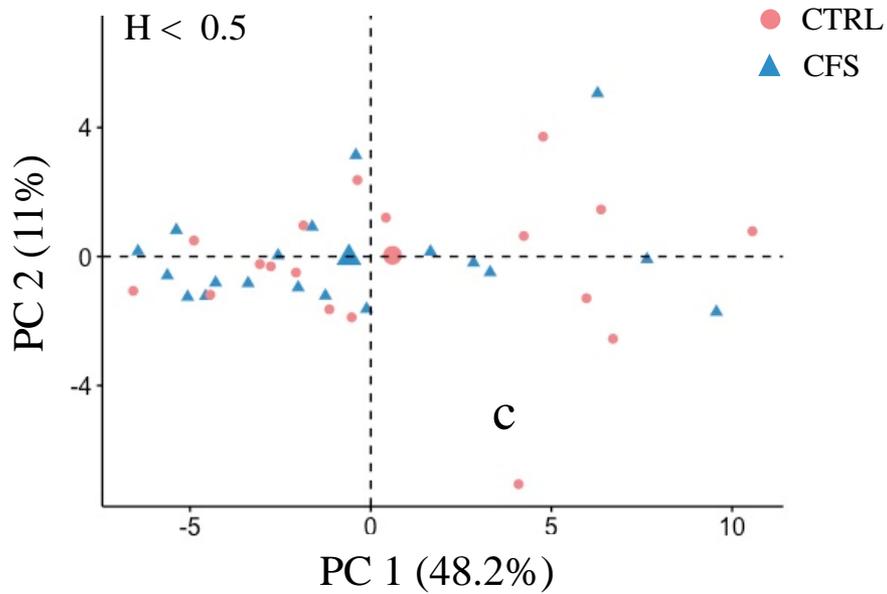
45 cytokines



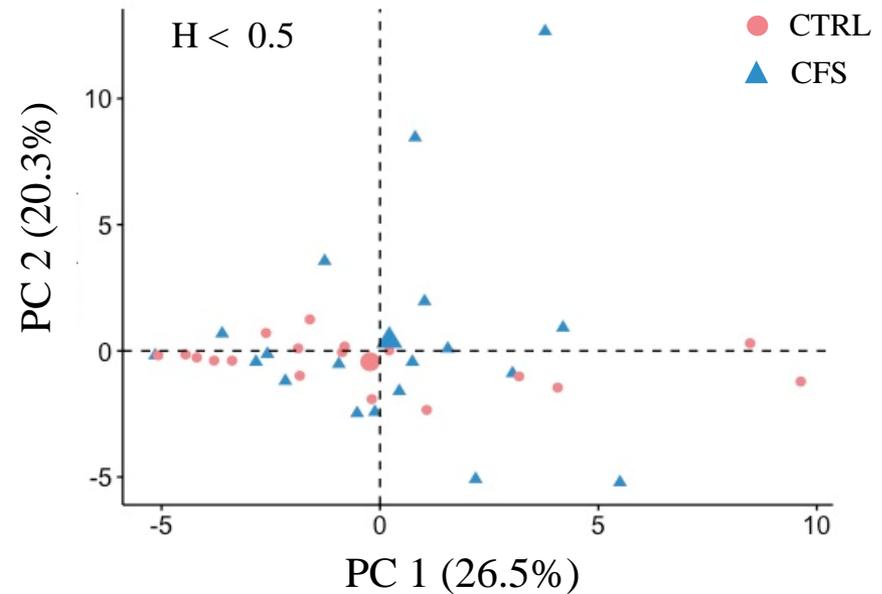
- G-CSF
- GM-CSF
- Granzyme B
- IFN-alpha
- IFN-beta
- IFN-gamma
- IL-1 alpha
- IL-1 beta
- IL-1ra/IL-1F3
- IL-2
- IL-3
- IL-4
- IL-5
- IL-6
- IL-7
- CCL2/MCP-1
- CCL3/MIP-1 alpha
- CCL4/MIP-1 beta
- CCL5/RANTES
- CCL11/Eotaxin
- CCL19/MIP-3 beta
- CCL20/MIP-3 alpha
- CD40 Ligand
- CX3CL1/Fractalkine
- CXCL1/GRO alpha
- CXCL2/GRO beta
- CXCL10/IP-10
- EGF
- FGF basic
- Flt-3 Ligand
- IL-8/CXCL8
- IL-10
- IL-12 p70
- IL-13
- IL-15
- IL-17A
- IL-17E/IL-25
- IL-33
- PD-L1/B7-H1
- PDGF-AA
- PDGF-AB/BB
- TGF-alpha
- TNF-alpha
- TRAIL
- VEGF

Principal component analysis does not separate cytokines present in patients vs. controls

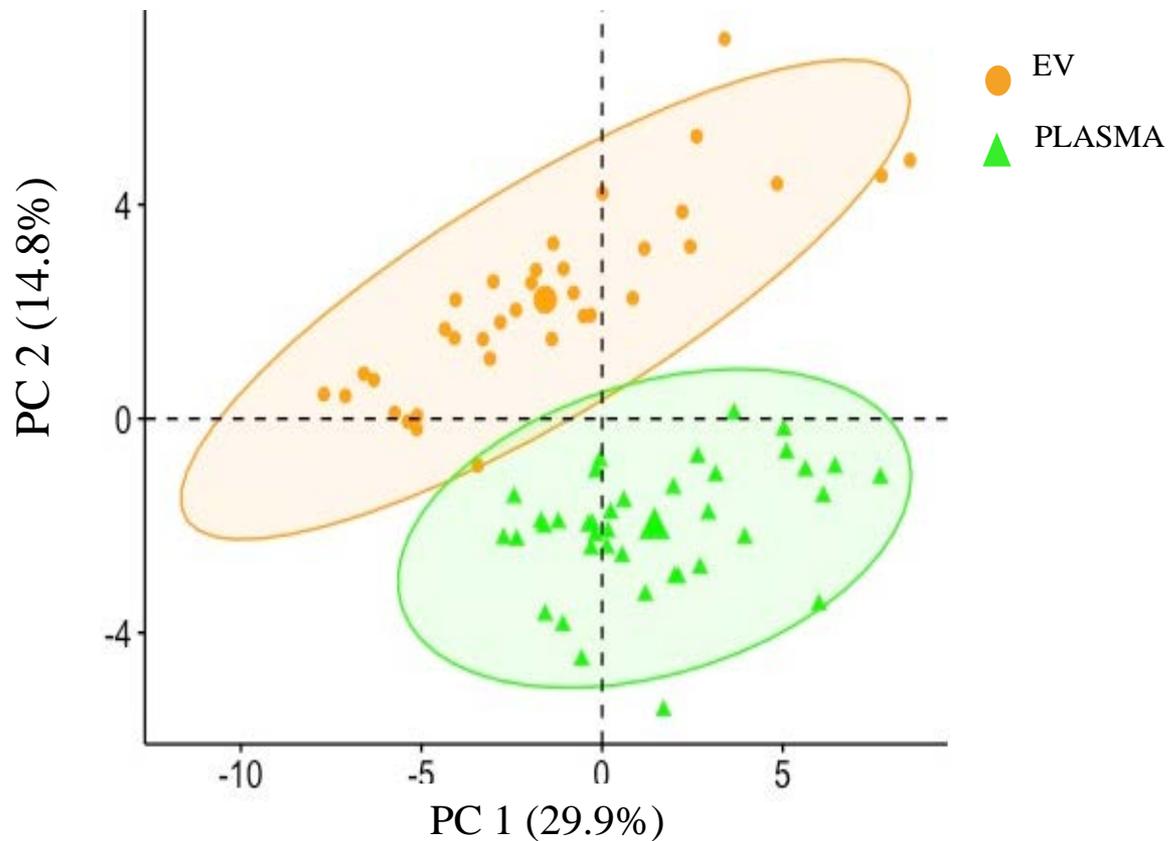
Plasma



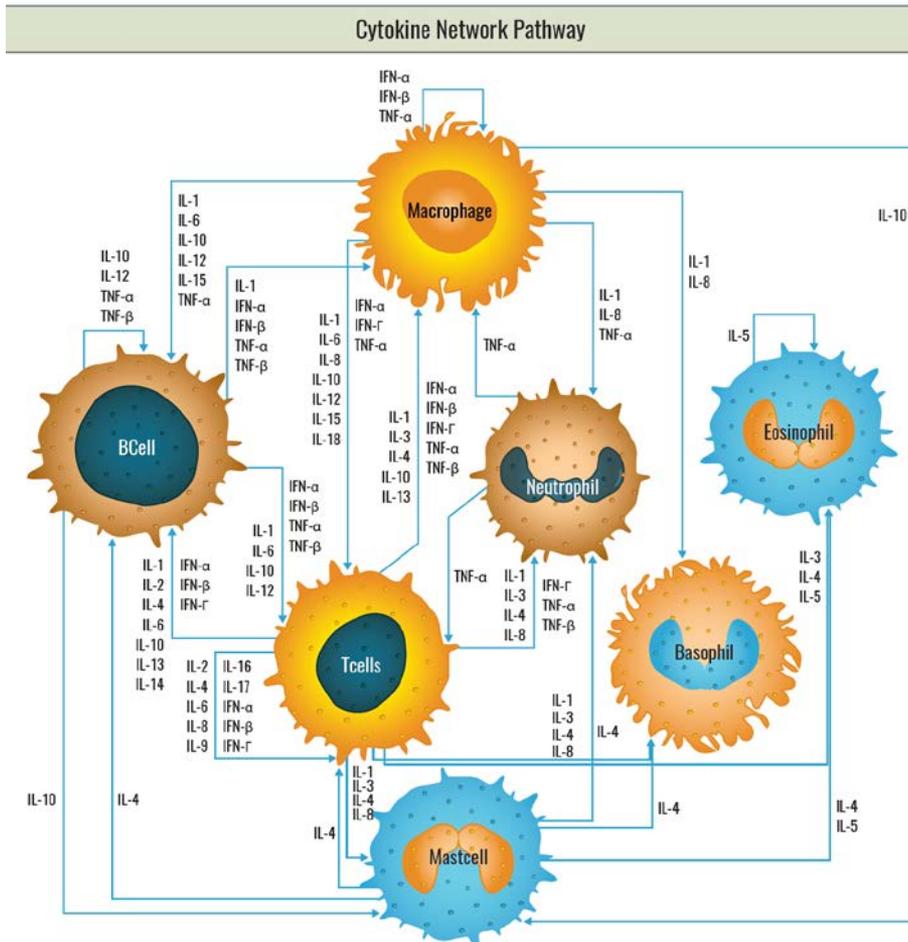
Extracellular Vesicles



Principal component analysis does separate cytokines present in plasma vs extracellular vesicles



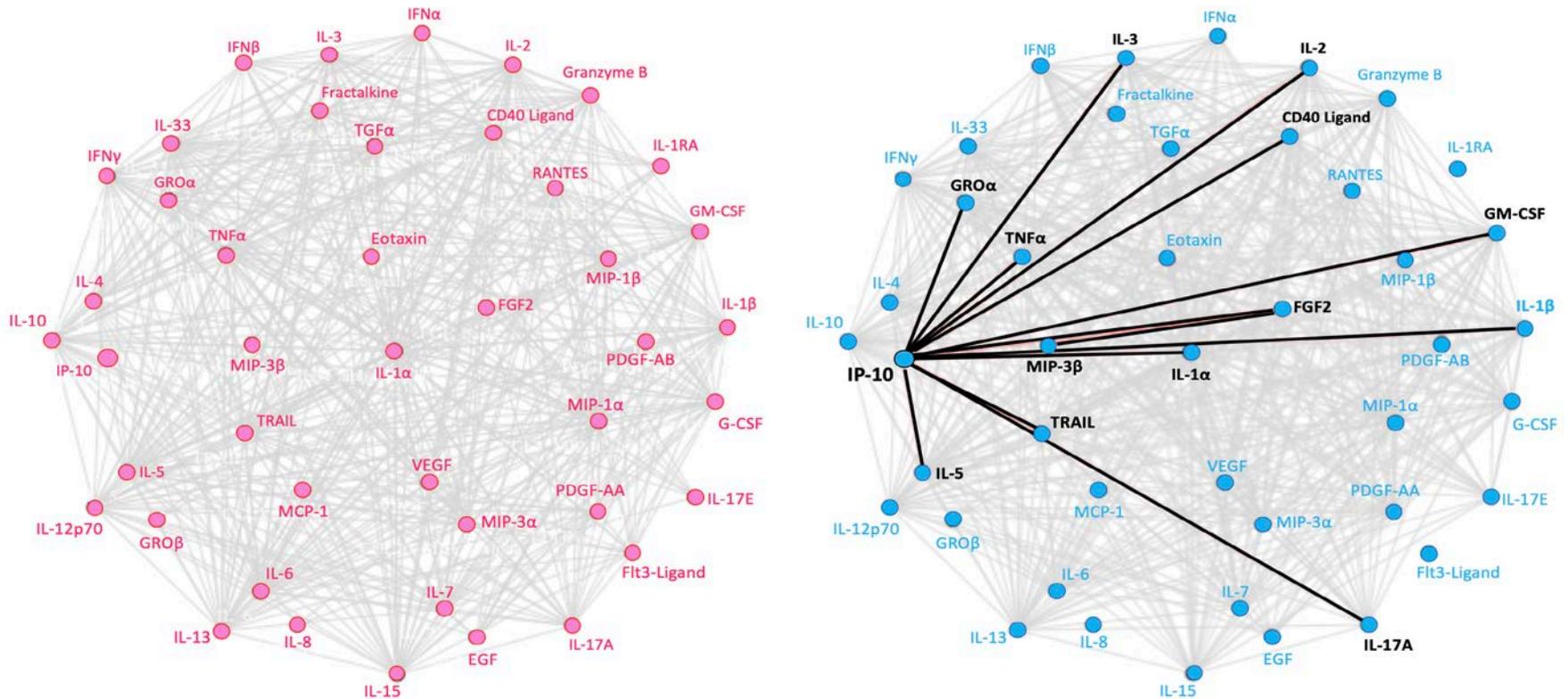
Are cells communicating normally through cytokines?



When a particular cytokine's level is high, is another cytokine's level also high?

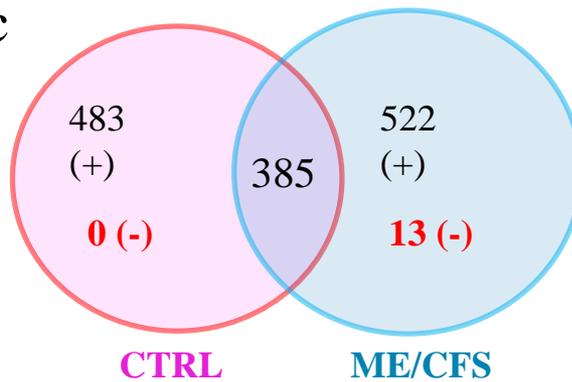
Or when a particular cytokine's level is high, is another cytokine's level low?

Dysregulation of cytokine-cytokine interactions in plasma



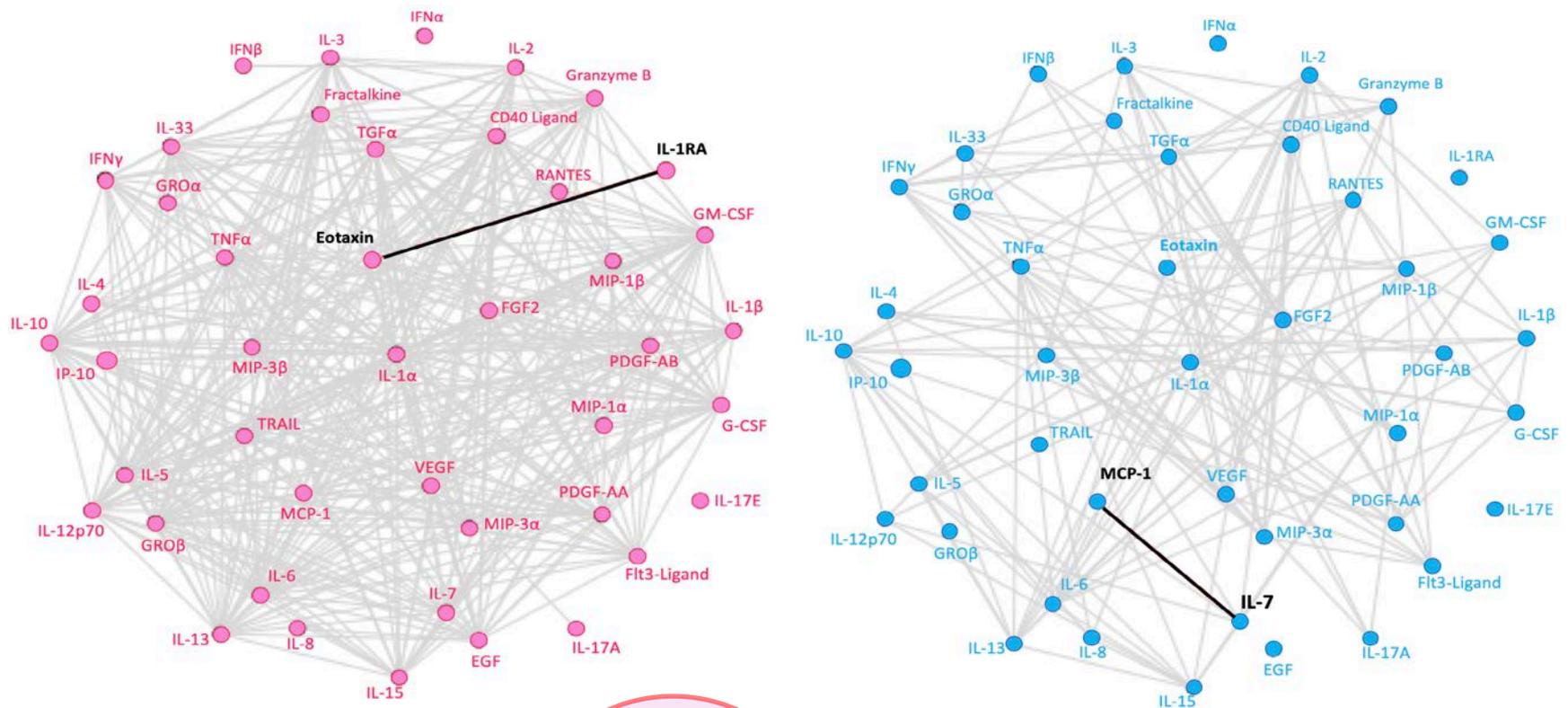
C

- positive correlations
- negative correlations

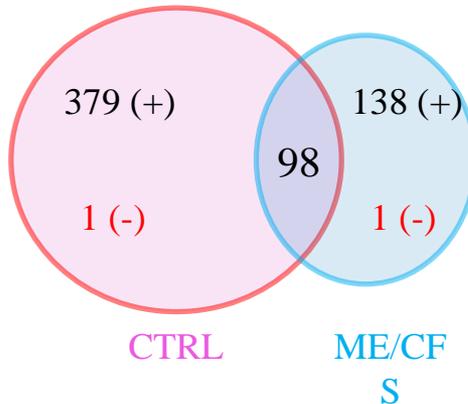


IP-10 involved in numerous ME/CFS negative correlations

Dysregulation of cytokine-cytokine interactions in EVs



C



— positive correlations
 — negative correlations

Many fewer positive correlations between cytokines in ME/CFS

Conclusions of pilot extracellular vesicle study

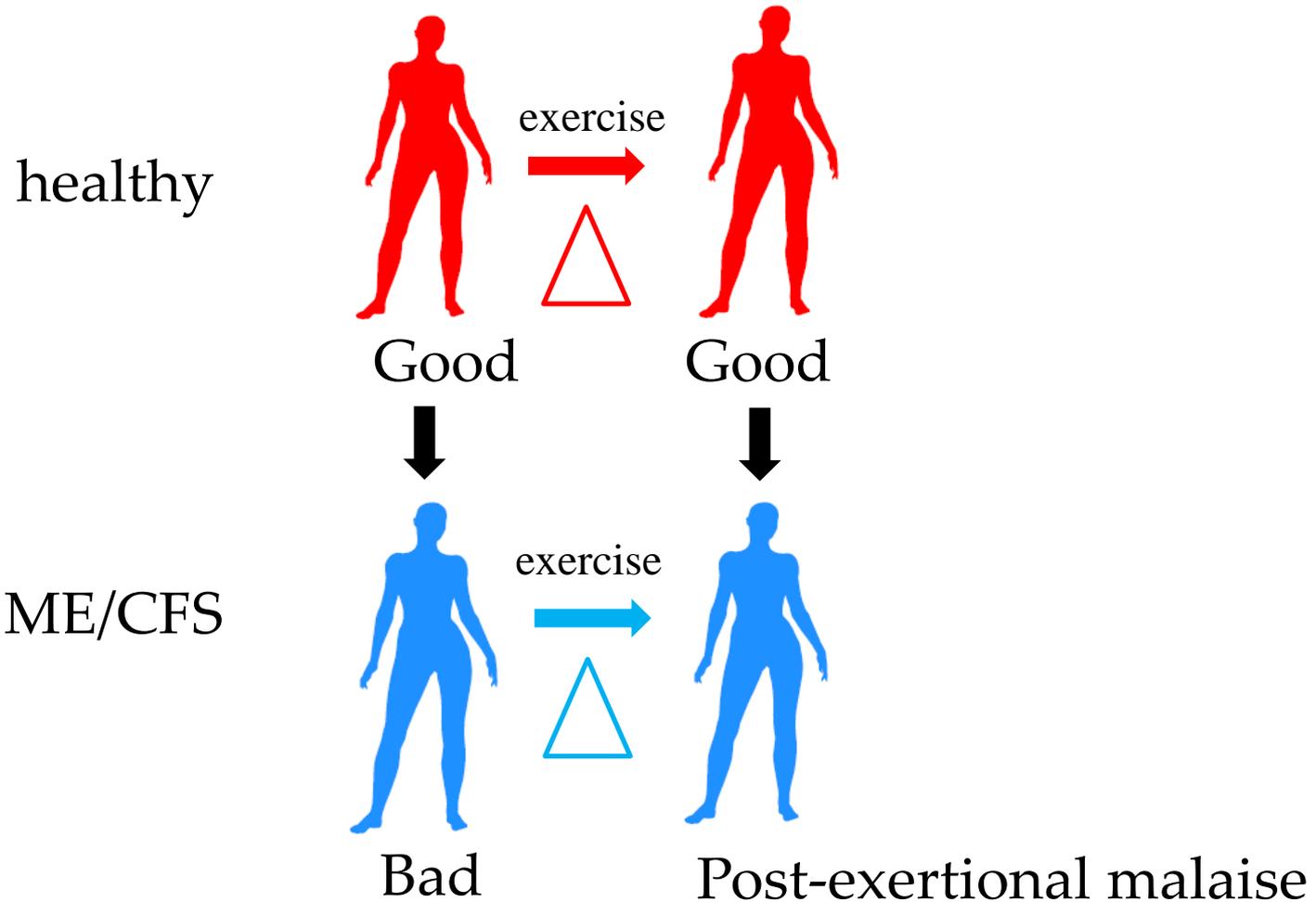
- No difference in EV size between ME/CFS and controls
- Significant increase in the concentration of 30-130 nm particles in ME/CFS
- No significant differences in the cytokine levels in plasma and EVs between groups
- Dysregulation of intercytokine associations in both plasma and EVs

Cytokine profiling of extracellular vesicles isolated from plasma in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: a pilot study

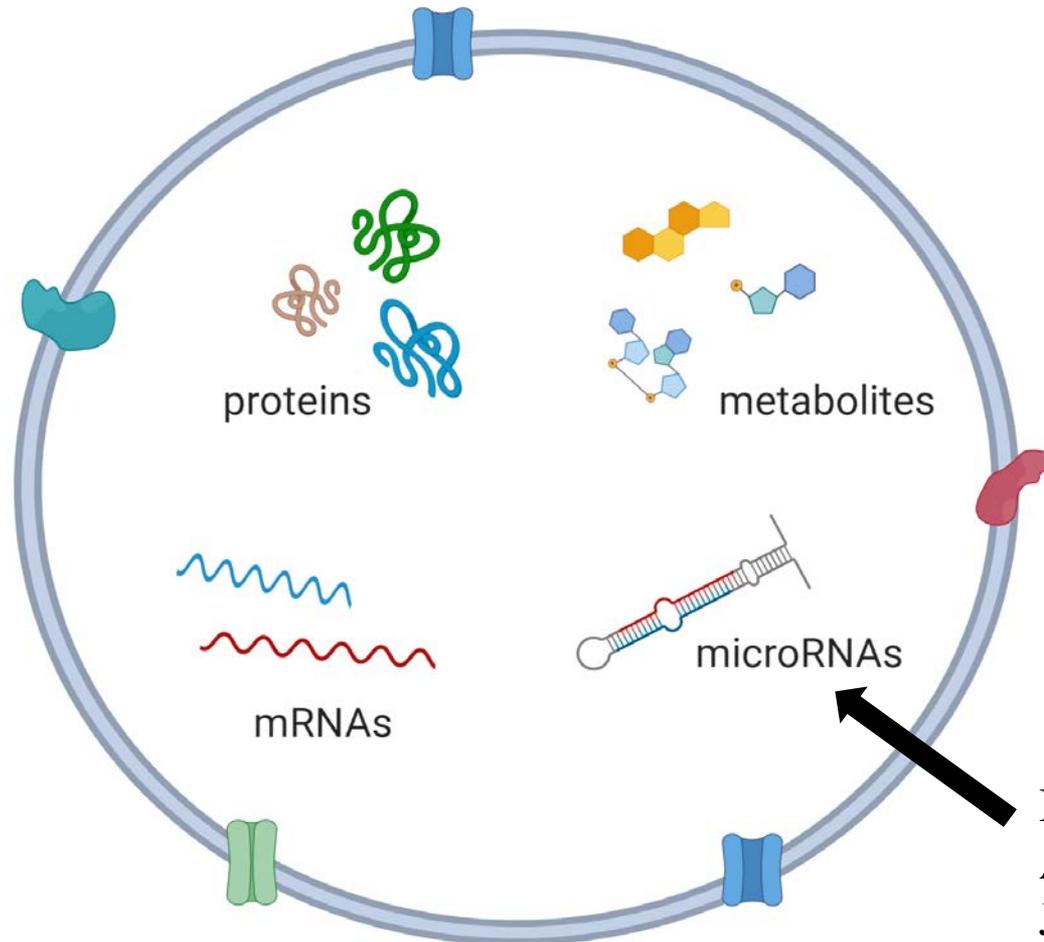
Ludovic Giloteaux, Adam O'Neal, Jesús Castro-Marrero, Susan M. Levine and Maureen R. Hanson

Under Review

Our current studies use samples before and after a provocation

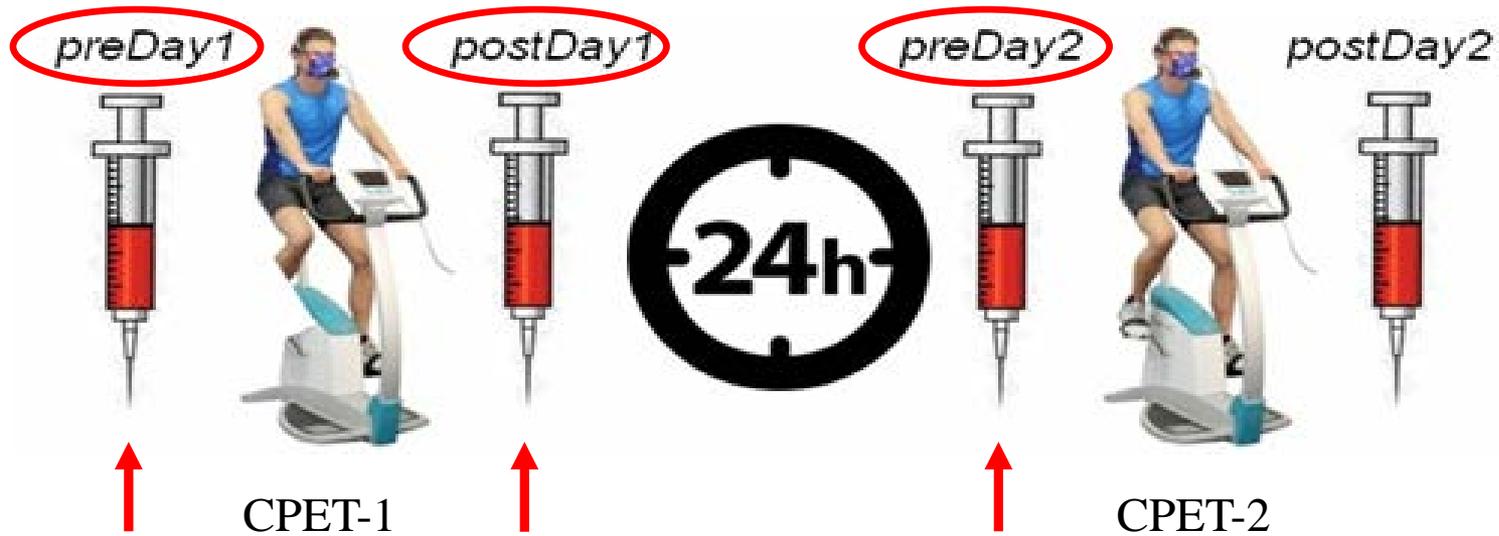


How does the cargo carried by extracellular vesicles change before and after exercise?



In progress
Andrew Grimson
Jen Grenier

Preliminary cytokine data from exercise subjects



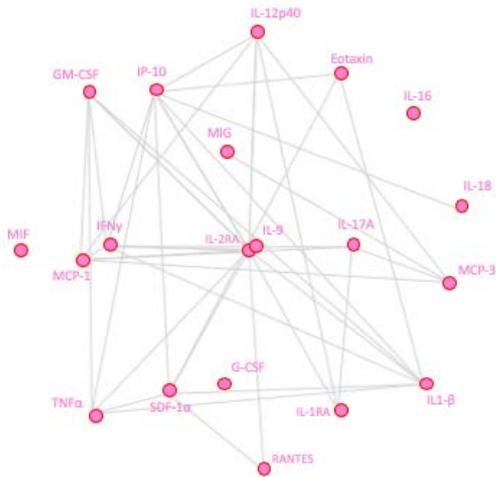
22 ME/CFS

17 Controls

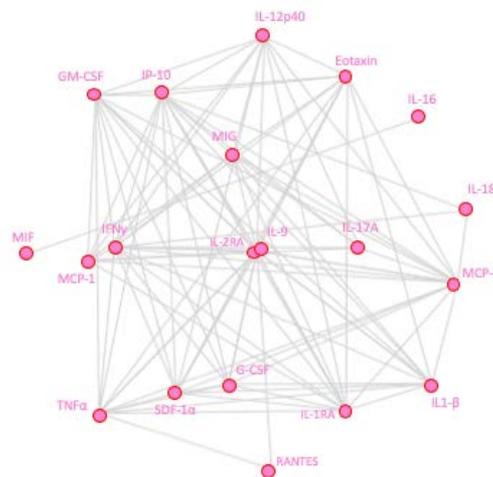


Exercise affects EV intercytokine cargo correlations

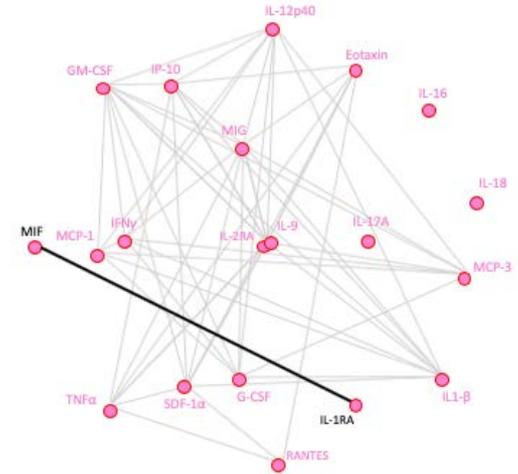
Controls preDay1



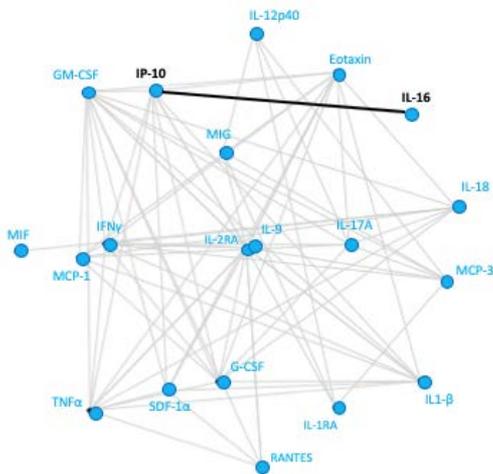
Controls postDay1



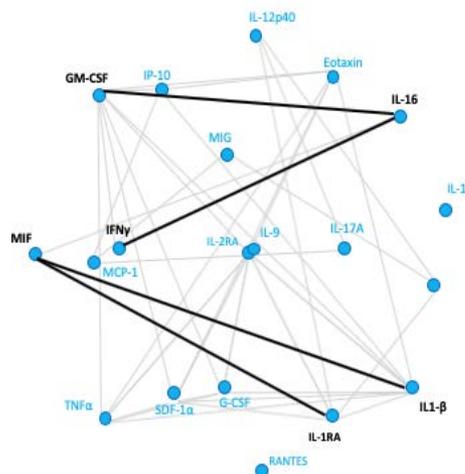
Controls preDay2



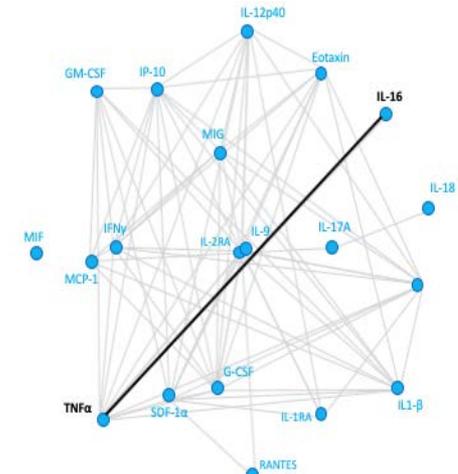
ME/CFS preDay1



ME/CFS postDay1



ME/CFS preDay2



Other types of protein cargo are being analyzed by mass spectrometry



90 samples

15 ME/CFS preDay1, postDay1, preDay2 = 45

15 controls preDay1, postDay1, preDay2 = 45

194 proteins total detected in EVs

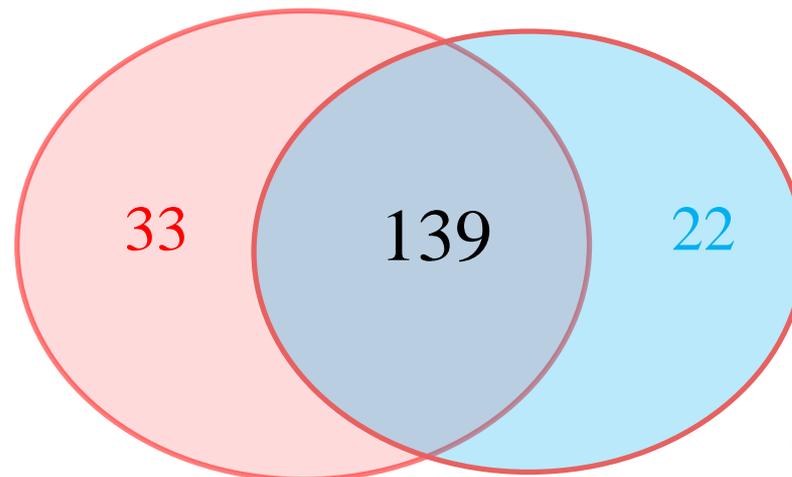
139 in common

33 in controls only

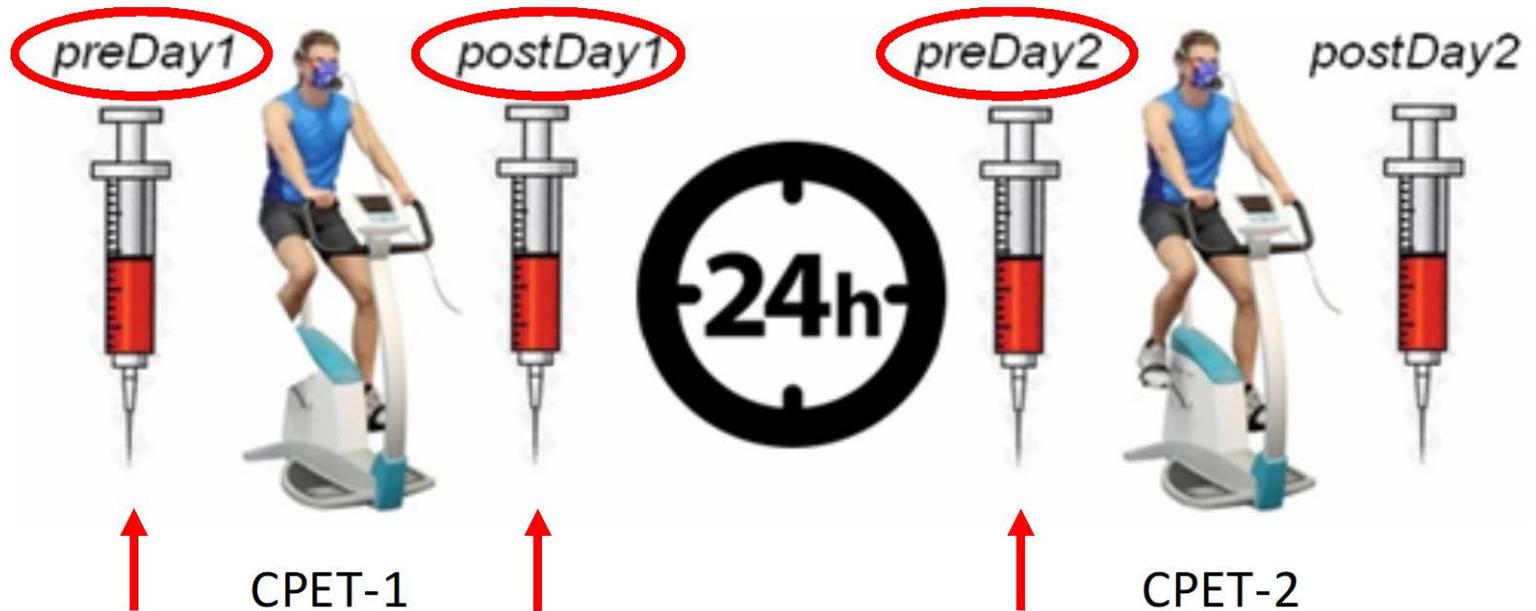
22 in ME/CFS only

Controls

ME/CFS



Differential protein content in control vs ME/CFS EVs increases with exercise



ME/CFS

34 proteins
lower than
in controls

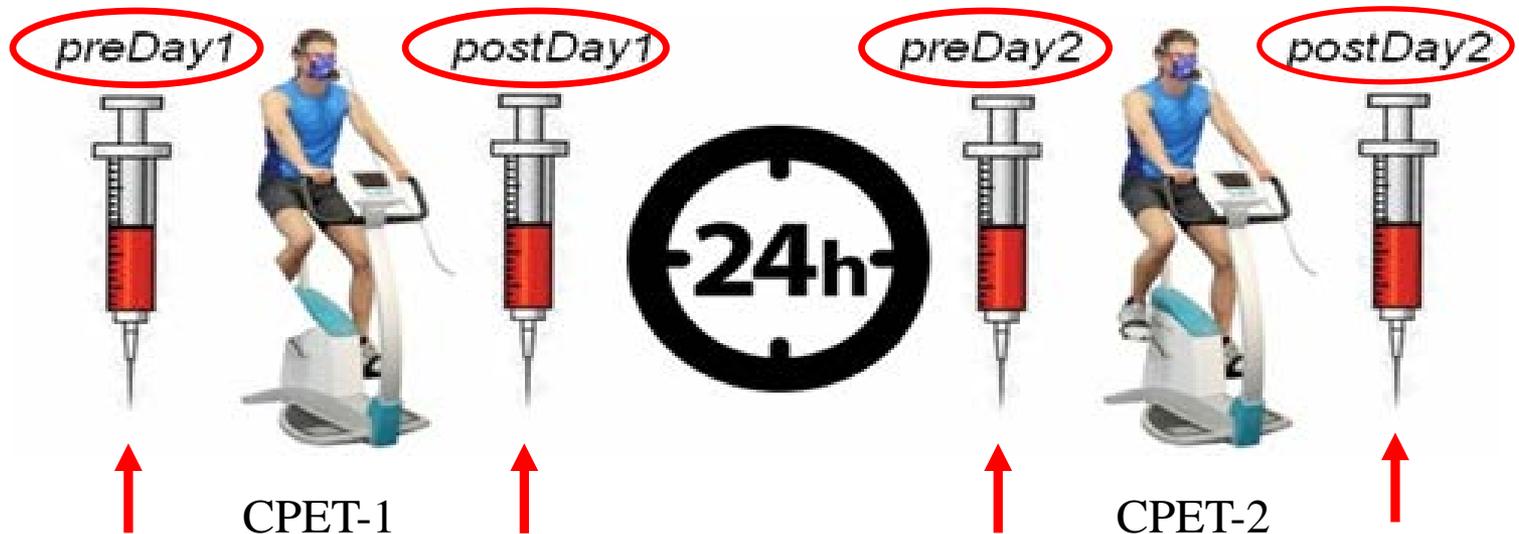
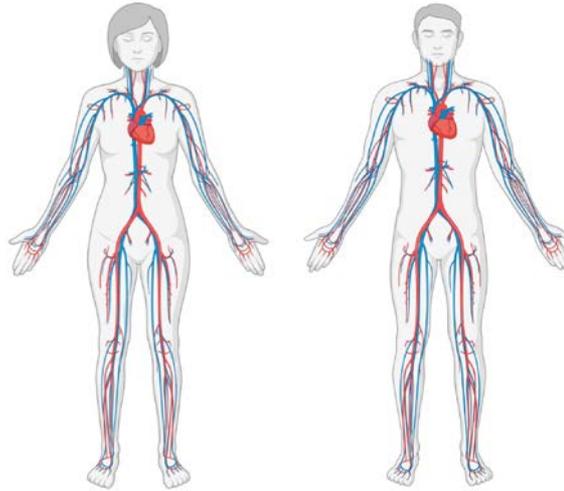
57 proteins
lower than in
controls

1 higher

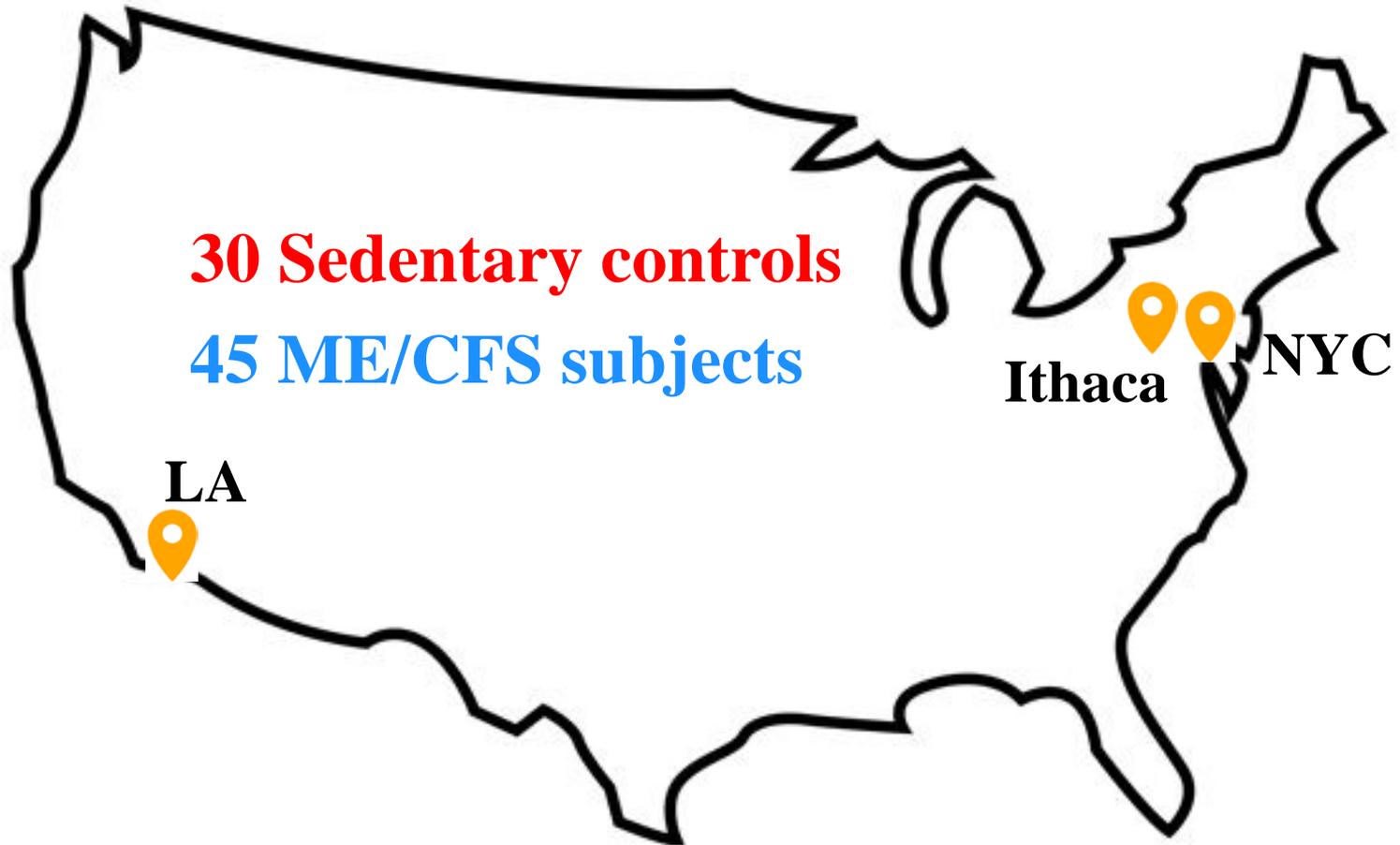
73 proteins
lower than
in controls

1 higher

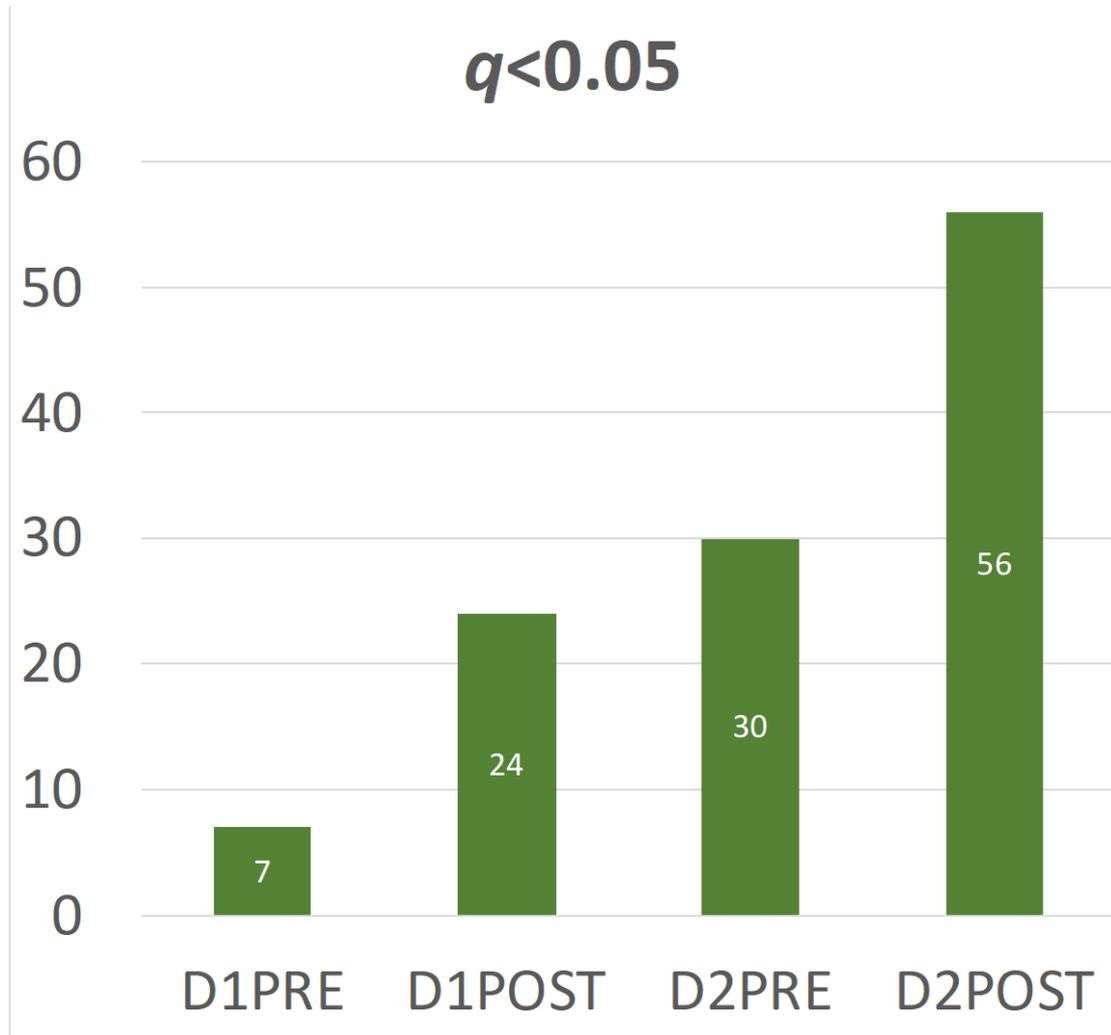
Plasma metabolite comparisons may reveal differences in functioning of tissues and organs



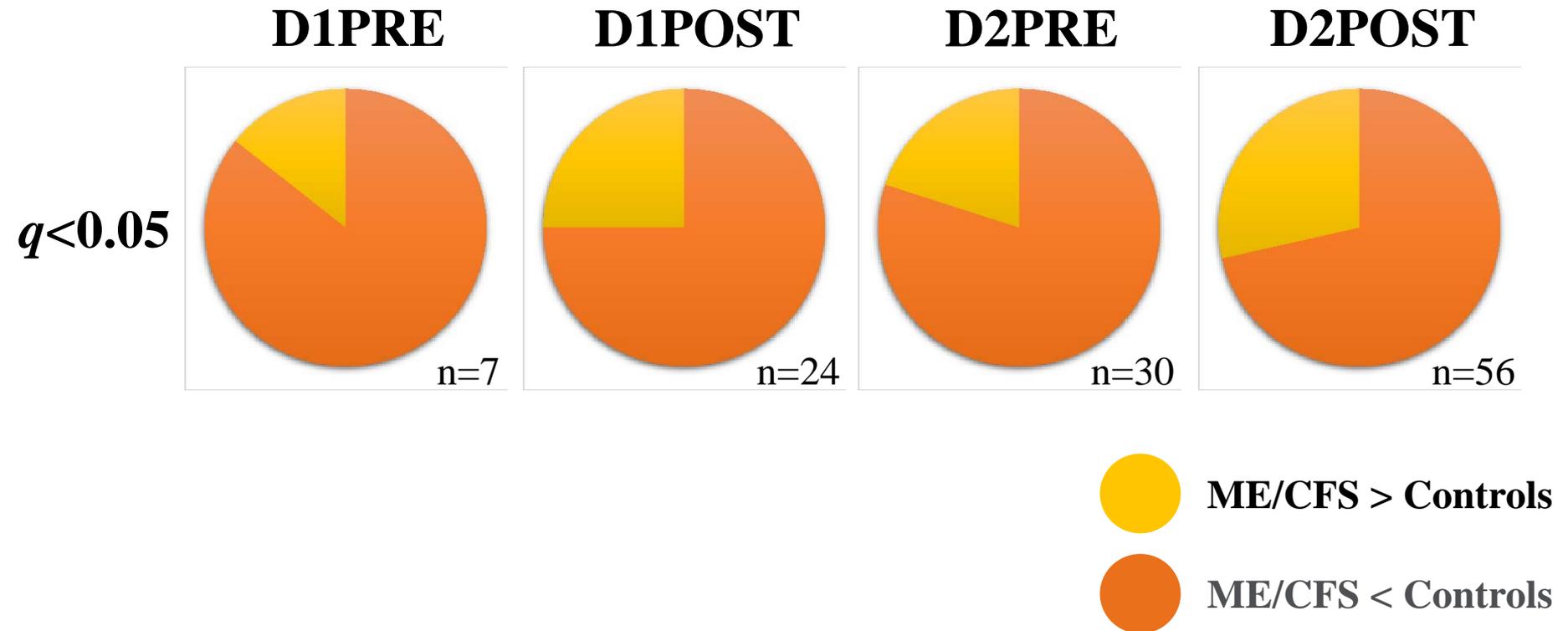
Plasma metabolites analyzed by Metabolon



Exercise increases the number of metabolites significantly different between controls and patients

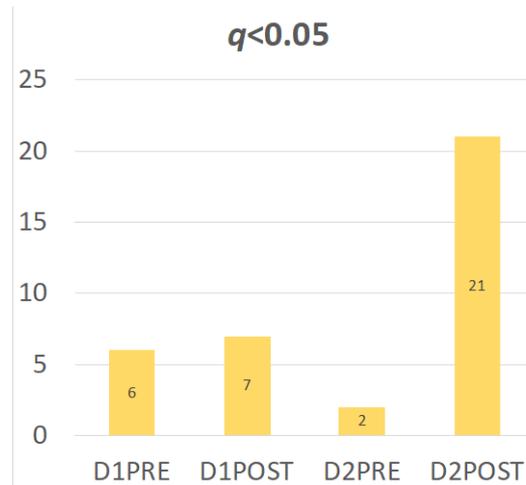


The majority of metabolites are lower in ME/CFS vs. Controls



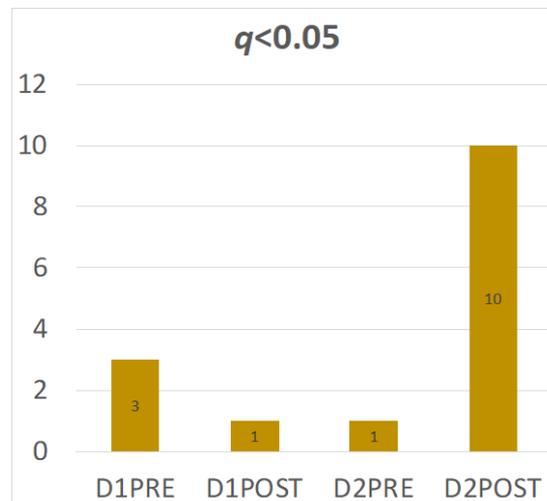
Number of lipids and fatty acids in ME/CFS that are higher than in controls greatly increases after the second CPET

Lipid Species



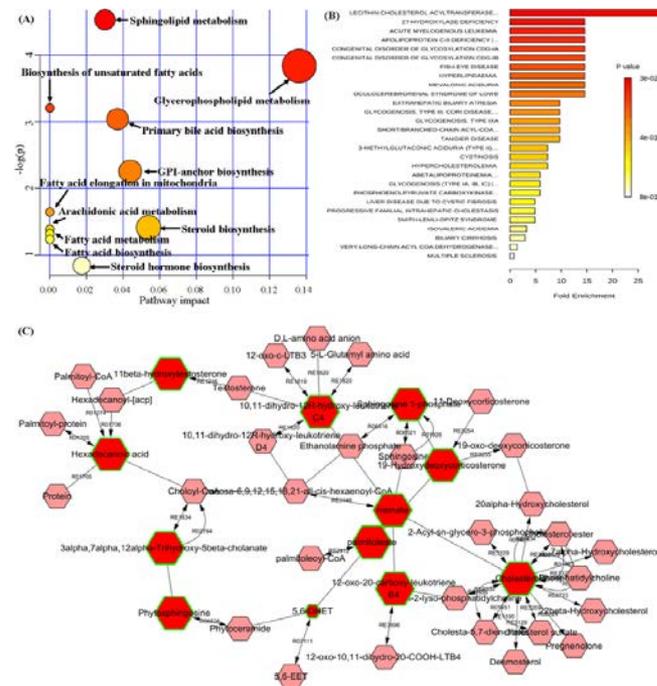
100%
ME/CFS > Controls

Fatty acids



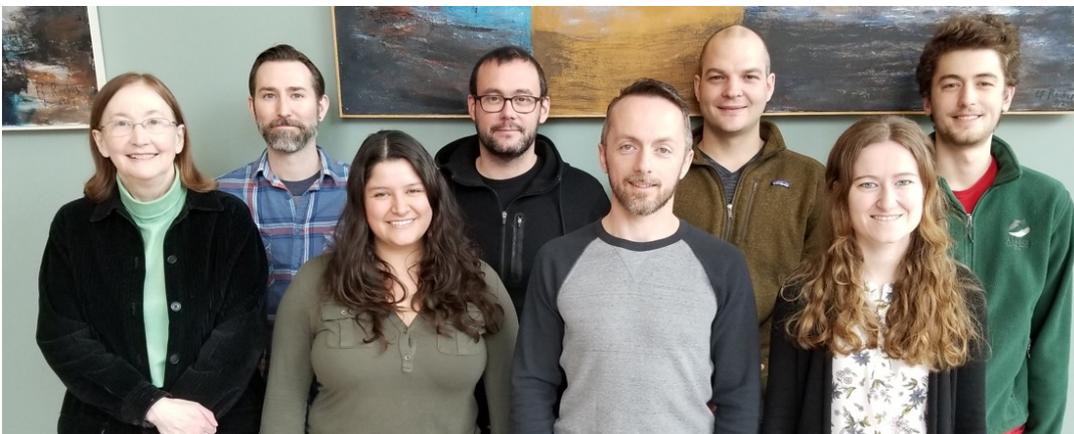
Work in Progress

Pathway Analysis



Integration of physiological measures and clinical information

Acknowledgments



The Hanson Lab Biomedical Group

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Jessica Maya
Ludovic Giloteaux
Arnaud Germain
Adam O'Neal
Alex Mandarano
Ivan Falstyn
Madeline McCanne
Vivian Huang

Jesús Castro-Marrero

Metabolon, Inc.
Cornell proteomics: Sheng Zhang



Simmaron Research
Scientifically Redefining ME/CFS

Daniel Peterson
Gunnar Gottschalk
Marco Maynard
Ivan Falstyn
Jineet Patel

Cornell NIH Center

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



Cornell University
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Private donors
Simmaron Research

Center for Energating NeuroImmune Disease



Center for Energating NeuroImmune Disease



Cornell University in Ithaca, NY

Weill Cornell Medicine in Manhattan, NY

The Cambridge Dictionary defines "**Energating**" as:
adjective
causing you to feel weak and lacking in energy

About the Cornell ENID Center

Foremost among cryptic neuroimmune diseases is one variously known as Myalgic Encephalomyelitis or Chronic Fatigue Syndrome or Systemic Exertion Intolerance Disease. The Center's mission is to promote research to identify its cause(s), biomarkers, and pathophysiology in order to lead to prevention and effective treatments.

Patient-focused webinars available under News tab



Questions and Answers

If you have additional questions following the call, please email CDC at MECFSSEC@cdc.gov.