Center for Solutions for ME/CFS

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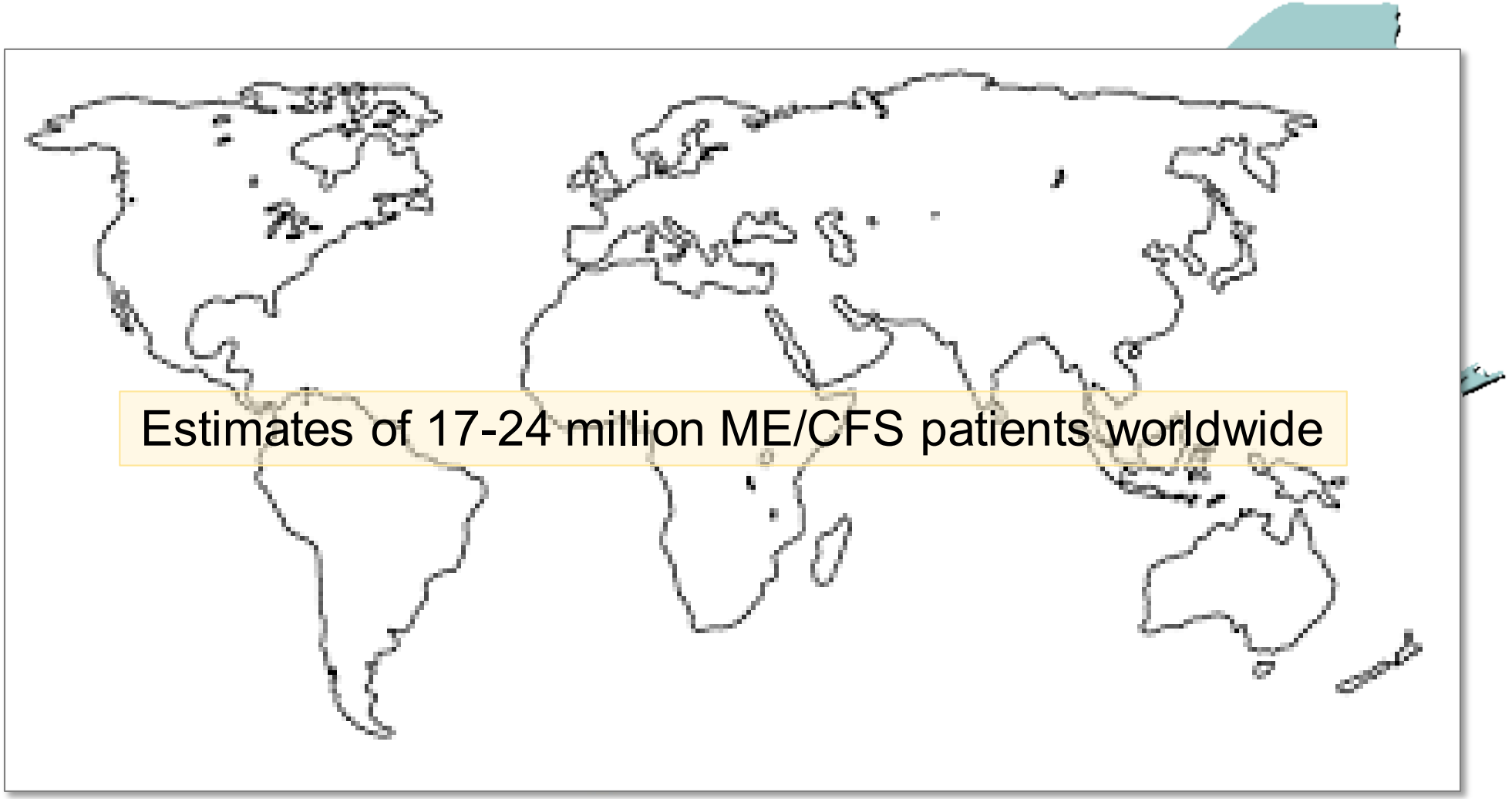
ME/CFS
Center for Solutions

ME/CFS Population



https://www.cdc.gov/me-cfs/about/index.html
https://ammes.org/how-many-people-have-mecfs/

The Burden of ME/CFS

DIAGNOSING AND TREATING MYALGIC ENCEPHALOMYELITIS/ CHRONIC FATIGUE SYNDROME (ME/CFS)

- U.S. ME/CFS CLINICIAN COALITION -
Version 2 · July 2020

ME/CFS studies have shown one peak of onset between ages 11-19 and a second between 30-39.

At least 25% of patients are bedbound or housebound and up to 75% are unable to work or attend school.

Symptoms can persist for years, and most patients never regain their pre-disease functioning

ME/CFS costs the US $17-$24 billion annually in lost productivity and direct medical costs.

What is Known About ME/CFS

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OF THE NATIONAL ACADEMIES

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KEY FACTS · FEBRUARY 2015
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

What are the symptoms and other effects of ME/CFS?

- Reduction or impairment in ability to carry out normal daily activities, accompanied by profound fatigue
- Post-exertional malaise
- Unrefreshing sleep
- Cognitive impairment
- Orthostatic intolerance

Immunological Abnormalities

Metabolic Disturbances

CDC

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HOPE Leading Research. Delivering Hope.

Prior Infections

Epstein-Barr virus
Ross River virus
Coxiella burnetti
} 11% develop ME/CFS symptoms

SARS
MERS
} 50% develop ME/CFS symptoms

Human herpesvirus 6
Enterovirus
Rubella
Candida albicans
Bornaviruses
Mycoplasma
Human immunodeficiency
} Infections studied but not found to be a cause of ME/CFS

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https://www.nap.edu/resource/19012/MECFS_KeyFacts.pdf
https://www.omf.ngo/2020/05/19/omf-funded-study-covid-19-and-me-cfs/
https://www.cdc.gov/me-cfs/about/possible-causes.html

ME/CFS
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What it's not:
XMRV

Final answer, Judy Mikovits (*left*) says she's "forever grateful" to Ian Lipkin (*right*), who led a big study of the link between XMRV and CFS.

RESEARCH ARTICLE

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

A Multicenter Blinded Analysis Indicates No Association between Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and either Xenotropic Murine Leukemia Virus-Related Virus or Polytropic Murine Leukemia Virus

Harvey J. Alter,[a] Judy A. Mikovits,[b] William M. Switzer,[c] Francis W. Ruscetti,[d] Shyh-Ching Lo,[e] Nancy Klimas,[f,g] Anthony L. Komaroff,[h] Jose G. Montoya,[i] Lucinda Bateman,[j] Susan Levine,[k] Daniel Peterson,[l] Bruce Levin,[m] Maureen R. Hanson,[n] Afia Genfi,[o] Meera Bhat,[o] HaoQiang Zheng,[c] Richard Wang,[a] Bingjie Li,[e] Guo-Chiuan Hung,[e] Li Ling Lee,[n] Stephen Sameroff,[o] Walid Heneine,[c] John Coffin,[p] Mady Hornig,[o] and W. Ian Lipkin[o]

Science

NEWS & ANALYSIS | INFECTIOUS DISEASES Martin Enserink

Science 21 Sep 2012:
Vol. 337, Issue 6101, pp. 1441-1442
DOI: 10.1126/science.337.6101.1441

New XMRV Studies Bring Closure—and Fresh Dispute

Summary
Most of the scientific community long ago pronounced dead the theory that a newly discovered gammaretrovirus dubbed XMRV, was linked to chronic fatigue syndrome. But the results of the biggest study of all had yet to come out. Funded by the U.S. National Institutes of Health and led by **Ian Lipkin of Columbia University**, the $1 million multi-center project finally published its results on Tuesday in *mBio* – and not surprisingly, **it concludes that the XMRV theory is really, really dead**. What *is* surprising, scientists say, is that **Judy Mikovits, the main author of the 2009 paper and the staunchest defender of a role for XMRV – or something closely related – is won over**.

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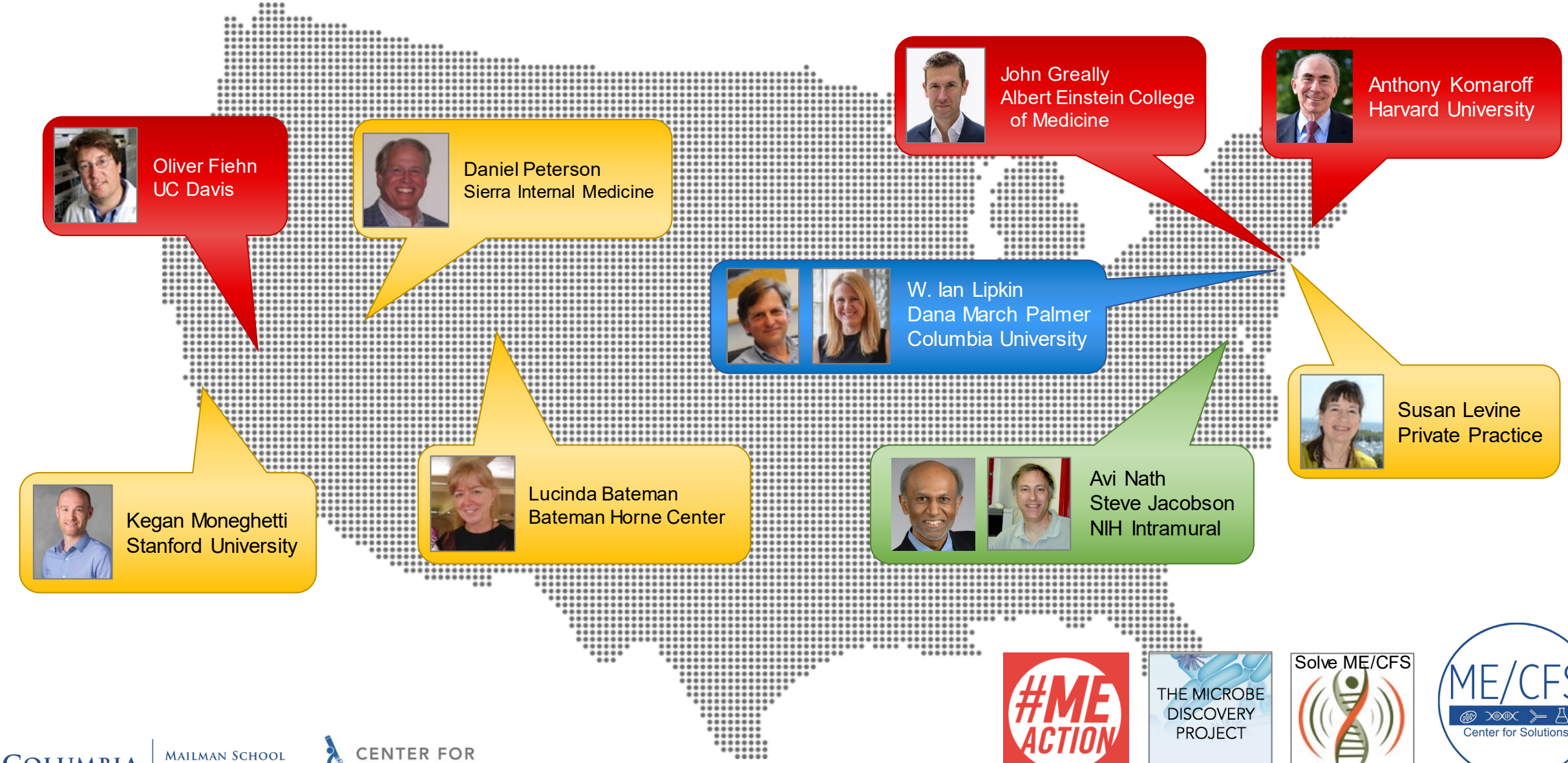
https://mbio.asm.org/content/3/5/e00266-12
https://science.sciencemag.org/content/337/6101/1441

Center for Solutions for ME/CFS (NIH)



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NIH Intramural

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#MEACTION

THE MICROBE DISCOVERY PROJECT

Solve ME/CFS Initiative

ME/CFS Center for Solutions

Highlights in the History of the CfS for ME/CFS

Journal of NeuroVirology (1999) 5, 495–499
© 1999 Journal of NeuroVirology, Inc.
http://www.jneurovirol.com

Absence of evidence of Borna disease virus infection in Swedish patients with Chronic Fatigue Syndrome

Birgitte Evengård*,[1], Thomas Briese[2], Gudrun Lindh[1], Shaun Lee[2] and W Ian Lipkin*,[2]

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SCIENTIFIC REPORTS

Insights into myalgic encephalomyelitis/chronic fatigue syndrome phenotypes through comprehensive metabolomics

Dorottya Nagy-Szakal[1], Dinesh K. Barupal[2], Bohyun Lee[1], Xiaoyu Che[1], Brent L. Williams[1],

RESEARCH ARTICLE

BIOMARKERS

Distinct plasma immune signatures in ME/CFS are present early in the course of illness

Mady Hornig,[1,2]* José G. Montoya,[3] Nancy G. Klimas,[4] Susan Levine,[5] Donna
Lucinda Bateman,[7] Daniel L. Peterson,[8] C. Gunnar Gottschalk,[8] Andrew F. Sc
Xiaoyu Che,[1] Meredith L. Eddy,[1] Anthony L. Komaroff,[9] W. Ian Lipkin[1,2,10]

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RESEARCH ARTICLE
DOI: 10.1128/mBio.00266-12

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BMC

Research | Open Access | Published: 26 April 2017
Microbiome 5, Article number: 44 (2017)

Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome

Dorottya Nagy-Szakal, Brent L. Williams, Nischay Mishra, Xiaoyu Che, Bohyun Lee, Lucinda Bateman, Nancy G. Klimas, Anthony L. Komaroff, Susan Levine, Jose G. Montoya, Daniel L. Peterson, Devi Ramanan, Komal Jain, Meredith L. Eddy, Mady Hornig & W. Ian Lipkin

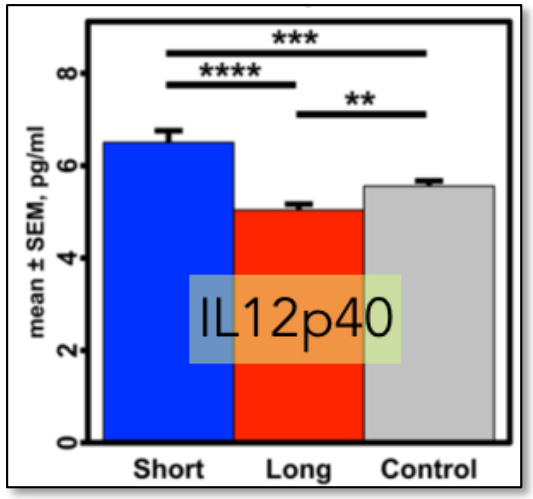
PLOS ONE

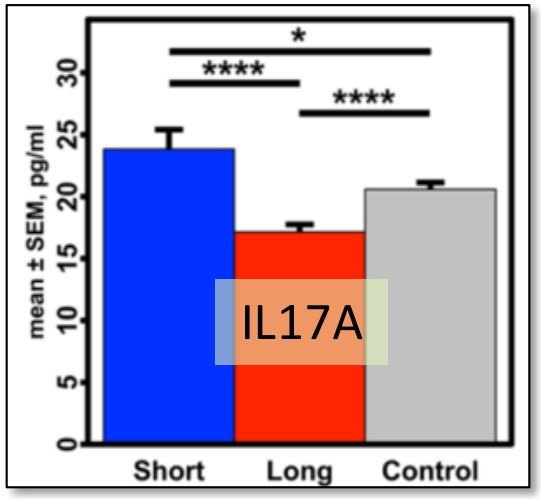
RESEARCH ARTICLE – July 21, 2020
https://doi.org/10.1371/journal.pone.0236148

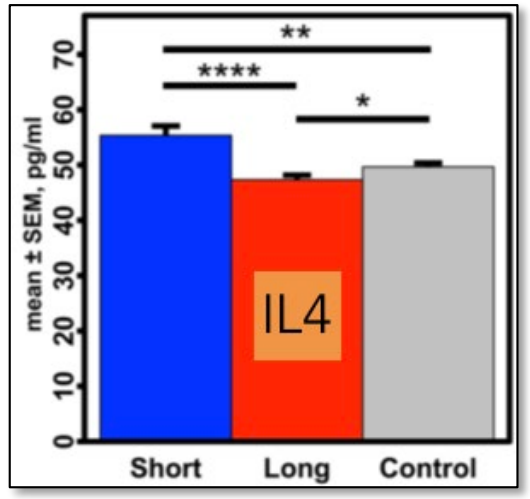
Plasma proteomic profiling suggests an association between antigen driven clonal B cell expansion and ME/CFS

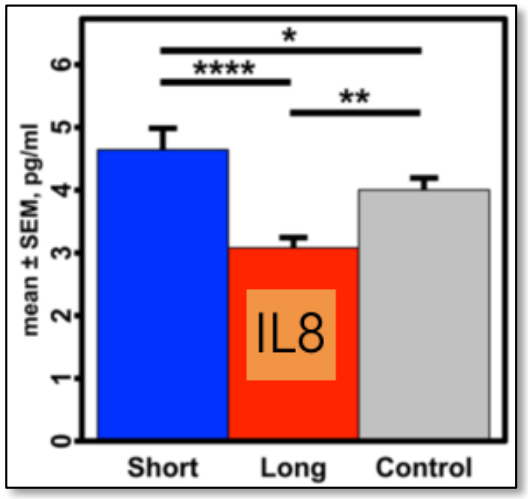
Milica Milivojevic, Xiaoyu Che, Lucinda Bateman, Aaron Cheng, Benjamin A. Garcia, Mady Hornig, Manuel Huber, Nancy G. Klimas, Bohyun Lee, Hyoungjoo Lee, Susan Levin, Jose G. Montoya, Daniel L. Peterson, Anthony L. Komaroff, W. Ian Lipkin

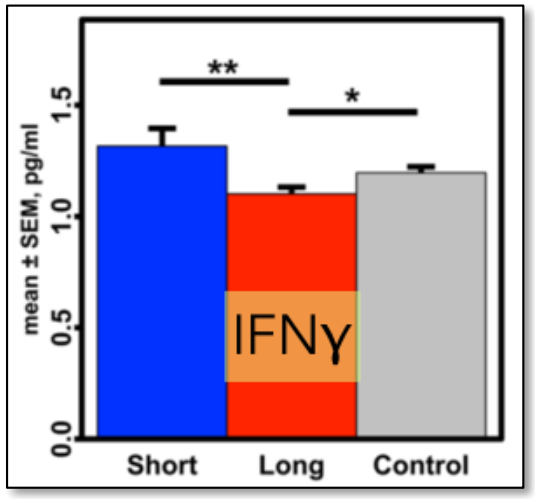
Timecourse for Cytokine Expression in *Plasma* in ME/CFS

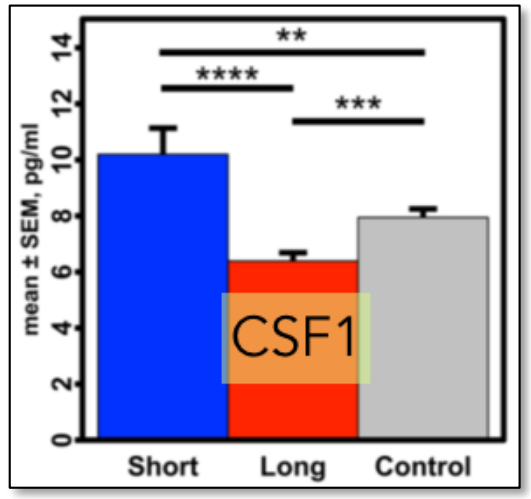












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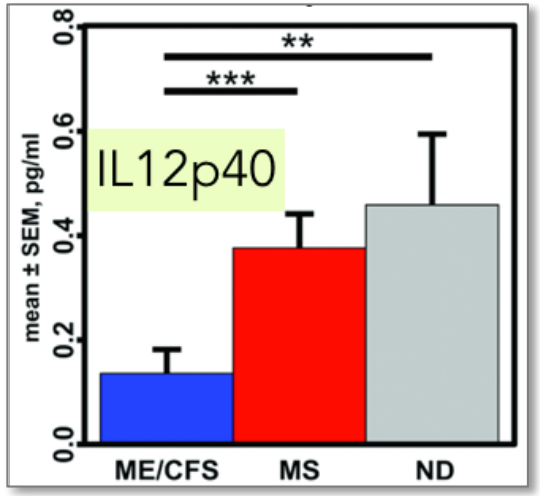
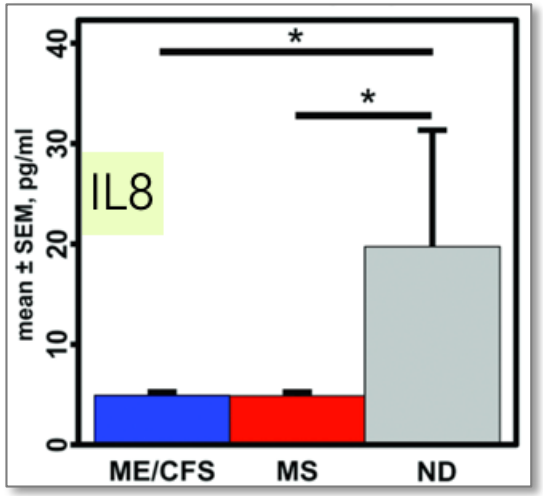
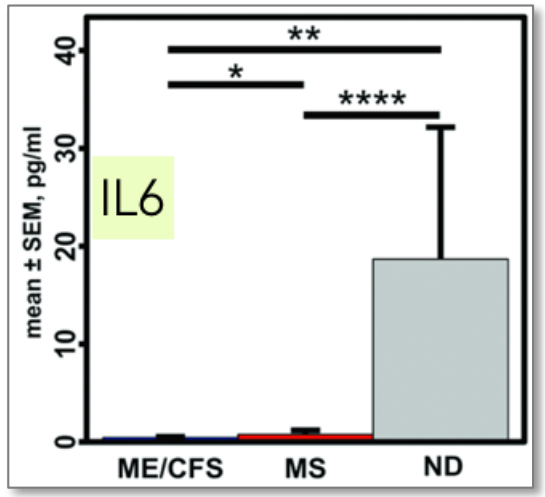
Hornig M, et al., Sci Adv 2015

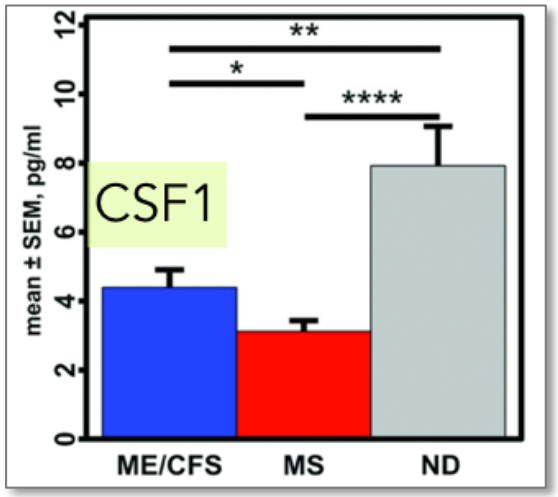
ME/CFS Center for Solutions

Cytokine Expression in *Cerebrospinal Fluid* in ME/CFS and Multiple Sclerosis









Hornig M, et al., Mol Psych 2015

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Metagenomics (Bacterial)

Fecal bacterial composition differs in ME/CFS vs healthy controls

Gut bacterial species and genera and their genes involved in butyrate production are decreased in ME/CFS patients

Fecal metabolomic analyses demonstrate that microbiome-derived butyrate levels (important in maintaining host health) are lower in ME/CFS patients

Deficiency in important butyrate producers in the gut

Species Associated with ME/CFS vs. Controls

id	Estimate.MECFS	Unadjusted p-value	FDR Adjusted p-value
Eubacterium rectale	-0.6734	0.000010	0.00046***
Faecalibacterium prausnitzii	-0.6234	0.000011	0.00046***
Gemmiger formicilis	-0.5044	0.000905	0.02474*
Fusicatenibacter saccharivorans	-0.4130	0.002347	0.04812*
Odoribacter splanchnicus	-0.3929	0.003649	0.05984
Roseburia intestinalis	-0.4139	0.004895	0.06690
Eubacterium hallii	-0.3730	0.006484	0.07596
Roseburia faecis	-0.4200	0.007605	0.07795
Roseburia hominis	-0.3882	0.009218	0.08399
Dorea longicatena	-0.3995	0.010665	0.08745
Barnesiella intestinihominis	-0.3913	0.017176	0.12804
Lachnospiraceae bacterium GAM79	-0.3447	0.021817	0.14054
Clostridium bolteae	0.3213	0.022281	0.14054
Flavonifractor plautii	0.3143	0.024443	0.14317
Roseburia inulinivorans	-0.2958	0.030891	0.16887
Coprococcus comes	-0.3056	0.040423	0.20717

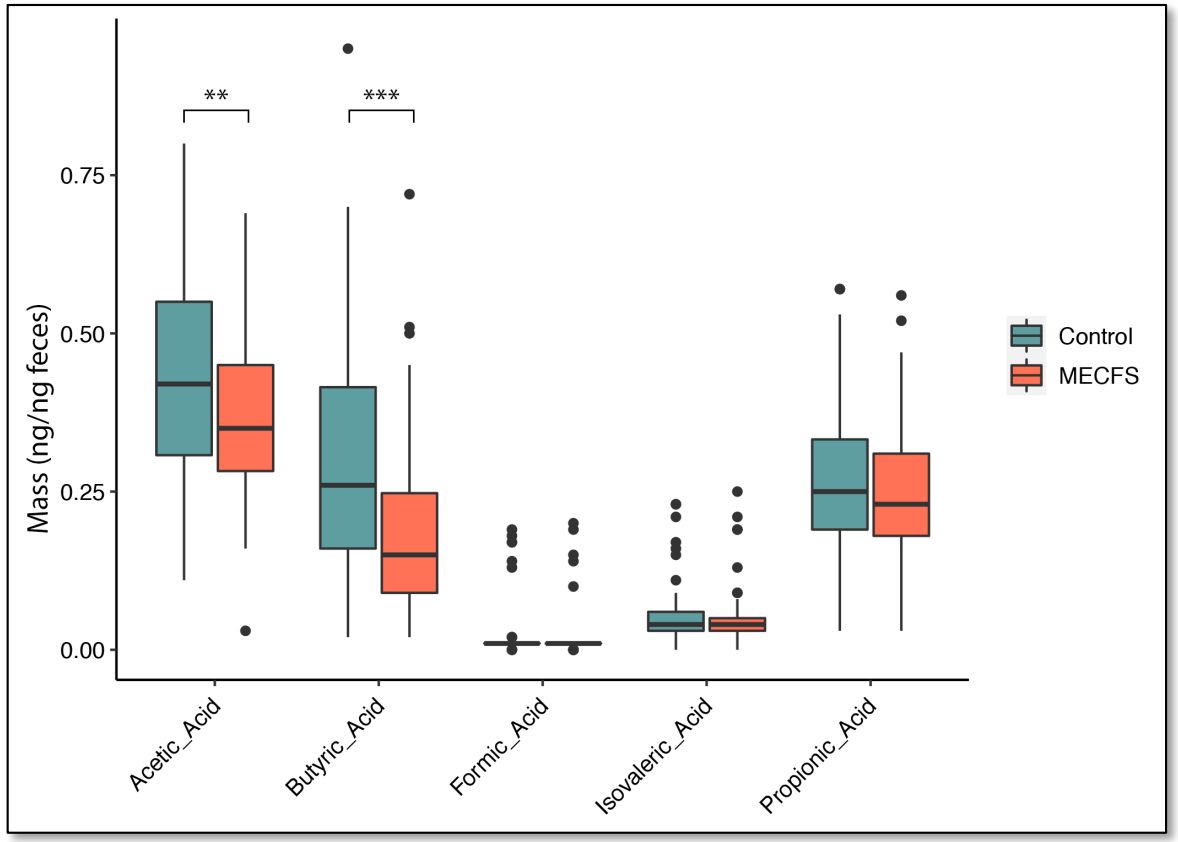
Genera Associated with ME/CFS vs. Controls

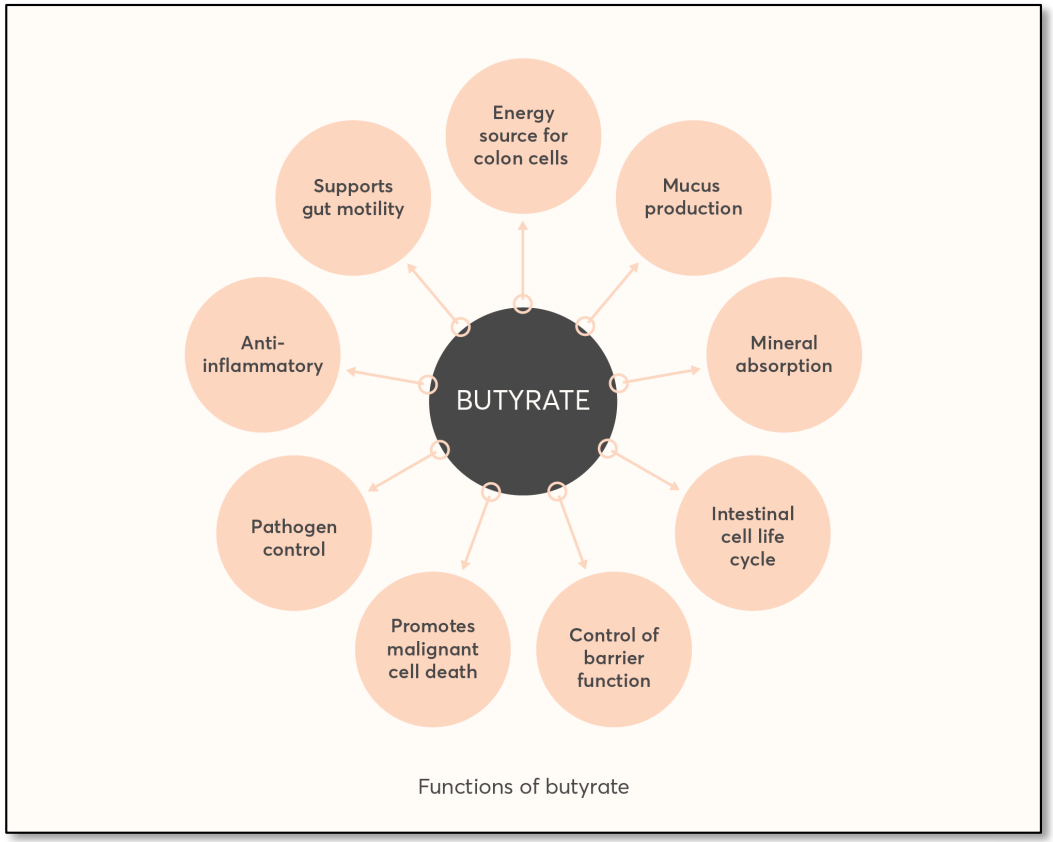
id	Estimate.MECFS	Unadjusted p-value	FDR Adjusted p-value
[Eubacterium]	-0.6734	0.000010	0.000279***
Faecalibacterium	-0.6234	0.000011	0.000279***
Dorea	-0.4880	0.000553	0.007235**
Roseburia	-0.4672	0.000579	0.007235**
Gemmiger	-0.5044	0.000905	0.009053**
Fusicatenibacter	-0.4130	0.002347	0.018674*
Eubacterium	-0.3817	0.002614	0.018674*
Lachnoclostridium	0.3505	0.005344	0.033399*
Ruminococcus	-0.3473	0.013708	0.076154
Barnesiella	-0.3818	0.017034	0.078383
Coprococcus	-0.3574	0.017244	0.078383
Flavonifractor	0.3143	0.024443	0.094012
Odoribacter	-0.2827	0.041442	0.148006

Model adjusted for sr-IBS, sex, age, site, BMI, race/ethnicity, season, antibiotics (6-12wk), probiotic supplements, prebiotic supplements

Fecal Short Chain Fatty Acids:

ME/CFS patients have deficient Acetate and Butyrate compared to controls, but only butyrate deficiency is independent of SR-IBS status





* p <0.05, ** p <0.01, *** p < 0.001, + with sr-IBS, - Without sr-IBS

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Plasma Proteomics

ME/CFS is associated with alterations in plasma levels of specific immunoglobulins

- IGHV3-23/30: OR = 4.439; p-value = 0.0182
- IGKV3(D)-11: OR = 4.527; p-value = 0.032
- IGHV3-23/30: OR = 4.545; p-value = 0.019

PLOS ONE

RESEARCH ARTICLE – July 21, 2020
https://doi.org/10.1371/journal.pone.0236148

Plasma proteomic profiling suggests an association between antigen driven clonal B cell expansion and ME/CFS

Milica Milivojevic, Xiaoyu Che, Lucinda Bateman, Aaron Cheng, Benjamin A. Garcia, Mady Hornig, Manuel Huber, Nancy G. Klimas, Bohyun Lee, Hyoungjoo Lee, Susan Levin, Jose G. Montoya, Daniel L. Peterson, Anthony L. Komaroff, W. Ian Lipkin

IGHV3-23/30

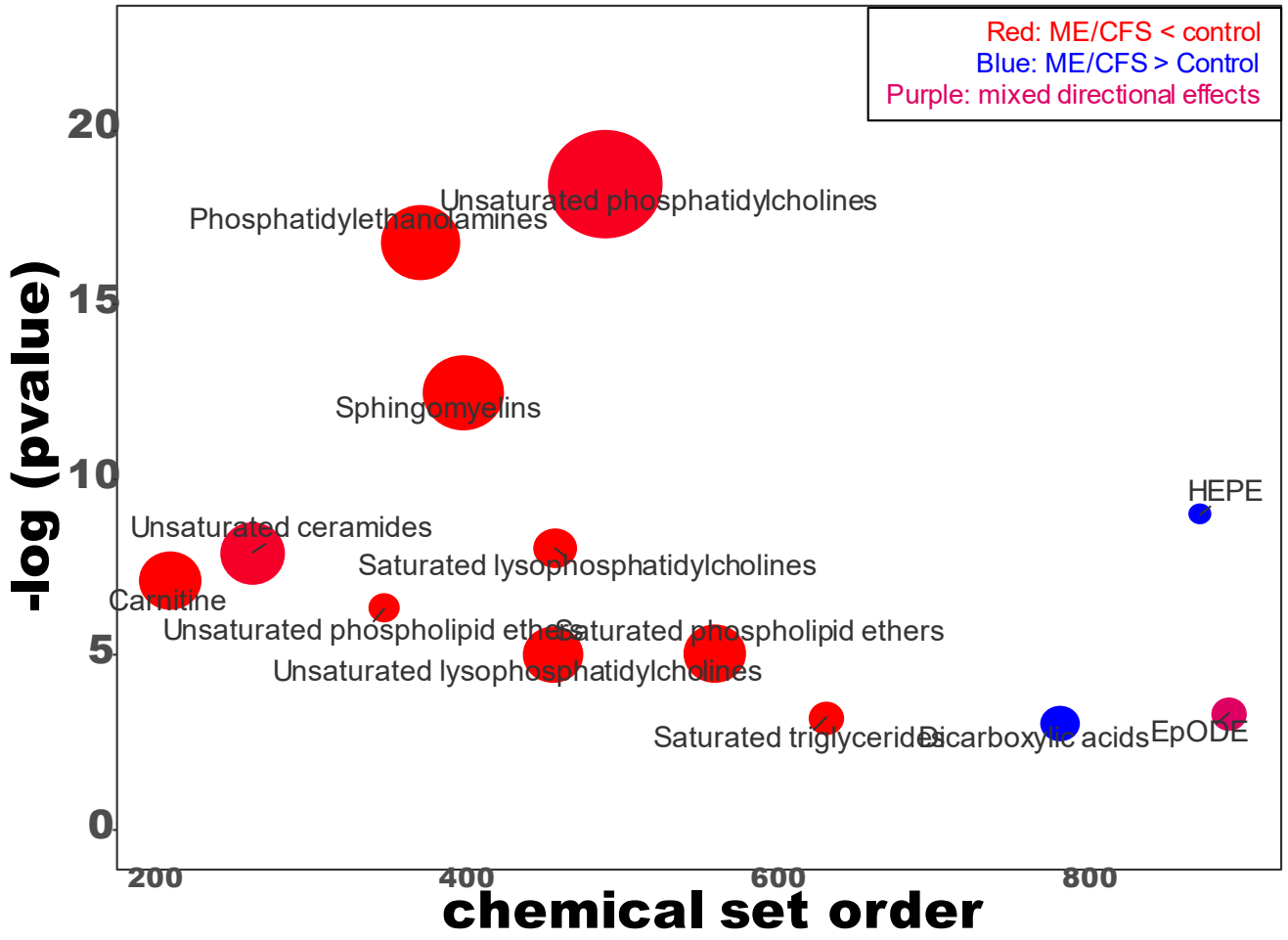
- Associations to lymphomas, anti-myelin associated glycoprotein neuropathy
- Induction: chronic stimulation from either microbial or auto-antigens
- Therapeutic implications: identify and remove stimulant, use kinase inhibitors
- ME/CFS patients are at an increased risk for lymphoma

Predictive modeling through biomarker analysis

- Altered levels: CAMP, IGLV1-47, LRG1, IGF1, GSN, IGFALS, FCRL3, SERPINA3

Metabolomic Analyses p<0.05

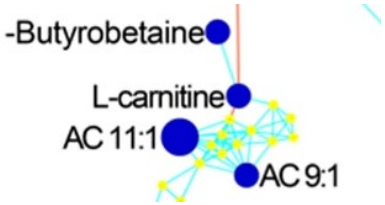
(ChemRICH, set enrichment statistics)



Metabolic Implications

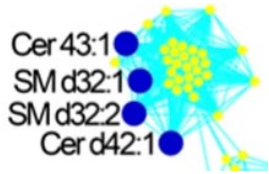
Mitochondrial dysfunction

Acylcarnitines ↓ , e.g. AC5:0a,b
TCA ↑ , e.g. succinate, alpha-ketoglutarate
FFA ↑ , e.g. 20:0, 16:1



Metabolic mediators

SM, Ceramides ↓
RvD1, PGF2a, PGD2, 8(9)EET ↓
12-HEPE, 15-HEPE, 17,18-DiHETE, 11(12)EET ↑

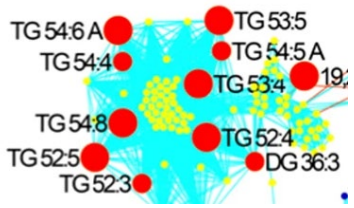


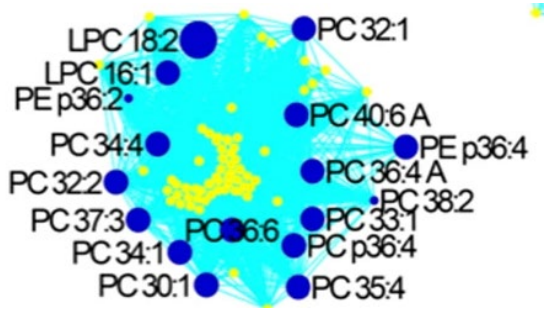
Exposure compounds

Less coffee & pepper consumption: ↓
caffeine, theobromine, trigonelline, piperine
Higher vegetables intake: ↑
trihydroxyisoflavone, choline
Higher medication: ↑
acetaminophen (pain), alprazolam (anxiety),
ranitidine (GI-comorbidity, heartburn),
acyclovir (sores), albendazole (infection)

Lipid metabolism

PUFA-plasmalogens ↓
PUFA-phosphatidylcholines ↓
PUFA-TGs ↑





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Therapeutics – Ampligen

A. Increase in Exercise Treadmill Duration with Rintatolimod in CFS Patients (Intent-to-Treat)

Study Interval	Mean (SD) Exercise Duration (Seconds)		Percent Increase from Baseline[1]		p-value
	Rintatolimod (n = 100)	Placebo (n = 108)	Rintatolimod (n = 100)	Placebo (n = 108)	
Baseline	576 (257.5)	588 (234.4)	-	-	0.729[2]
Week 40	672 (314.1)	616 (286.7)	36.5	15.2	0.047[3]
p-value[4]	-	-	<0.001	0.198	

B. Increase in Exercise Treadmill Duration with Rintatolimod in CFS Patients (Completer Population)

Study Interval	Mean (SD) Exercise Duration (Seconds)		Percent Increase from Baseline[1]		p-value
	Rintatolimod (n = 93)	Placebo (n = 101)	Rintatolimod (n = 93)	Placebo (n = 101)	
Baseline	583 (254.7)	587 (237.3)	-	-	0.908[2]
Week 40	691 (311.4)	614 (291.2)	40.2	15.6	0.019[3]
p-value[4]	-	-	<0.001	0.244	

C. Increase in Exercise Treadmill Duration with Rintatolimod in CFS Patients without Significant Dose Reductions (Intent-to-Treat)

Study Interval	Mean (SD) Exercise Duration (Seconds)		Percent Increase from Baseline[1]		p-value
	Rintatolimod (n = 83)	Placebo (n = 98)	Rintatolimod (n = 83)	Placebo (n = 98)	
Baseline	581 (256.2)	590 (235.3)	-	-	0.813[2]
Week 40	690 (308.2)	616 (291.4)	43.0	15.0	0.022[3]
p-value[4]	-	-	<0.001	0.263	

D. Frequency Distribution of Percent Change from Mean Baseline Exercise Treadmill Duration at Week 40 (Intent-to-Treat)

Improvement from Mean Baseline Exercise Treadmill Duration	Rintatolimod (n = 100)	Placebo (n = 108)	p-value[5]
At least 25%, n (%)	39 (39)	25(23)	0.013
At least 50%, n (%)	26 (26)	15 (14)	0.028

E. Effect of Baseline ET on Week 40 ET (Intent-to-Treat)

	Mean (SD) Exercise Duration Mean (seconds)				% Gain Rintatolimod over Placebo[1]		p-value[3]	
Baseline ET Strata (Minutes)	≤9 Drug (n = 40)	≤9 Placebo (n = 42)	>9 Drug (n = 60)	>9 Placebo (n = 66)	≤9	>9	≤9	>9
Baseline	321 (153.3)	353 (144.6)	747 (148.3)	738 (137.7)				
Week 40	450 (284.2)	446 (264.6)	820 (237.3)	725 (245.9)	31.0	15.0	0.517	0.034

[1]Mean intra-patient percent improvement.
[2]Student's t-test comparing mean baseline ET between treatment groups.
[3]Analysis of covariance (ANCOVA) with baseline as a covariate comparing the mean ET change from baseline within each treatment group.
[4]Paired t-test comparing whether the change from baseline is equal to zero within each treatment group.
[5]Probability that a difference between treatment groups exists using the chi-square test.
doi:10.1371/journal.pone.0031334.t001

PLOS ONE OPEN ACCESS PEER-REVIEWED RESEARCH ARTICLE
Published: March 14, 2012 · https://doi.org/10.1371/journal.pone.0031334

A Double-Blind, Placebo-Controlled, Randomized, Clinical Trial of the TLR-3 Agonist Rintatolimod in Severe Cases of Chronic Fatigue Syndrome

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At week 40, the rintatolimod patients had increased mean ET by 108 seconds (18.6%) to 691 compared to an increase of 27 seconds (4.6%) to 614 in the placebo cohort.

At 40 weeks, the difference in improvement in ET for the rintatolimod versus placebo cohorts in the pre-specified completer and ITT groups was statistically significant ($p = 0.019$ and 0.047, respectively) using an analysis of covariance model. A paired-difference t-test for analysis of the intra-patient difference from baseline provided additional evidence that rintatolimod produced a significant increase in ET for patients debilitated with CFS/ME. Both the completer and ITT populations improved ET significantly ($p < 0.001$) compared to the placebo cohorts ($p \geq 0.198$).

68% of patients receiving rintatolimod decreased use of concomitant medications related to CFS versus 55% of subjects receiving placebo ($P = 0.048$)

FDA Response Letter Regarding Approval of Ampligen for ME/CFS *February 6, 2013*

On Monday, February 4, 2013, Hemispherx announced the receipt of a Complete Response (CR) letter from the FDA for Ampligen. FDA issues a CR letter to convey that our review of an application is complete and we cannot approve the application in its present form. A CR letter describes all of the specific deficiencies that the Agency has identified in an application, allowing the company an opportunity to correct those clearly defined deficiencies in a re-submission.

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https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0031334
https://www.fdanews.com/ext/resources/files/archives/0/02/02-06-13-Ampligen.pdf

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Gulf War Illness

The National Academies of SCIENCES ENGINEERING MEDICINE

Date: April 9, 2010
FOR IMMEDIATE RELEASE
Gulf War Service Linked to Post-Traumatic Stress Disorder, Multisymptom Illness, Other Health Problems, But Causes Are Unclear

It is likely that multisymptom illness results from the interactions between environmental exposures and genes, and genetics may predispose some individuals to illness, the committee noted. There are sufficient numbers of veterans to conduct meaningful comparisons given that nearly 700,000 US personnel were deployed to the region and more than 250,000 of them suffer from persistent, unexplained symptoms. The committee concluded that multisymptom illness is linked to Gulf War service, based on the availability of a number of good-quality surveys documenting increased reporting and occurrence of multiple, unexplained symptoms among veterans.

U.S. Department of Veterans Affairs

Public Health: Gulf War Exposures

Gulf War Veterans may have been exposed to a variety of environmental and chemical hazards that carried potential health risks.

- Vaccinations: regionally required, anthrax, botulinum toxoid
- Pyridostigmine Bromide (PB): protection against nerve gas exposure
- Chemical Agent Resistant Coating (CARC) paint
- Oil well fires
- Chemical and biological weapons
- Sand, dust, and particulates
- Depleted Uranium
- Toxic Embedded Fragments
- Pesticides
- Noise
- Infectious Diseases
- Heat injuries
- Occupational hazards

Symptom	% Reported
Fatigue	23%
Headache	17%
Memory problems	32%
Muscle/joint pain	18%
Diarrhea	16%
Dyspepsia/indigestion	12%
Neurological problems	15%
Terminal tumors	33%

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https://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12835
https://www.publichealth.va.gov/exposures/gulfwar/sources/index.asp
https://www.va.gov/RAC-GWVI/Pre_2014_Committee_Documents.asp

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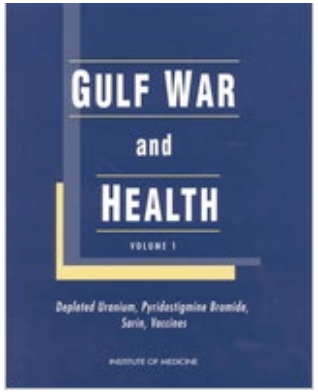
Gulf War Illness:
Insights into ME/CFS?

TABLE 7.1 Vaccinations Prescribed for Military Personnel

Disease or Agent	Army	Navy	Air Force	Marine Corps	Coast Guard
Adenovirus types 4 and 7	B	B	G	B	G
Vibrio cholerae	E	E	E	E	E
Hepatitis A	G	G	C,D	G	G
Hepatitis B	F,G	F,G	F,G	F,G	F,G
Influenza	A,B,X	A,B,R	A,B,R	A,B,R	B,C,G
Japanese Encephalitis	D	D	D	D	G
Measles	B,F	B,F	B,F	B,F	B,G
Meningococcus (types A, C, Y, W135)	B,D	B,D	B,D	B,D	B,G
Mumps	F,G	B,F,G	F,G	B,F,G	G
Polio	B,D,R	B,R	B,R	B,R	A
Plague	D,F	F	F	F	F
Rabies	F	F	F	F	G
Rubella	B,F	B,F	B,F	B,F	B
Tetanus-diphtheria	A,B,R	A,B,R	A,B,R	A,B,R	A,B
Typhoid	C,D	C,D	C,D	C,D	D
Varicella	F,G	F,G	F,G	G	F,G
Yellow fever	C,D	A,R	C,D	A,R	B,C,E

NOTE: A = All active-duty personnel; B = recruits; C = alert forces; D = when deploying or traveling to high-risk areas; E = only when required by host country for entry; F = high risk occupational groups; G = as directed by applicable surgeon general or Commandant, Coast Guard; R = reserve components; X = reserve component personnel on active duty for 30 days or more during the influenza season.

SOURCE: U.S. Department of the Air Force, 1995.



Gulf War and Health
Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide, Vaccines
Institute of Medicine (US) Committee on Health Effects Associated with Exposures During the Gulf War
ISBN-10: 0-309-07178-X

https://www.ncbi.nlm.nih.gov/books/NBK222854/#ddd00264

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PAHO

...nd sequelae of

COVID-19 Real-Time Learning Network
Brought to you by CDC and IDSA

Post-Acute COVID-19 Syndrome
Updated October 19, 2020

Persistent symptoms in patients after acute COVID-19 (Carfi, July 2020).

- Most common reported symptoms were **fatigue (53%)**, dyspnea (43%), arthralgias (27%) and chest pain (22%).

Post-discharge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation (Halpin, July 2020).

- New fatigue was the most common reported symptom.
- **72% of participants in the ICU group reported fatigue**, while 60.3% in the non-ICU group did.

Severe pneumonia requiring oxygen therapy

Pneumonia

Fever
Cough
Dyspnea
Myalgia or arthralgia
Odynophagia
Fatigue
Diarrhea
Headache

...ss syndrome

Coagulation disorders

...*enal, liver, heart*)

...ent

Neurology® Clinical Practice

Potential neurological manifestations of COVID-19

Anna S. Nordvig, Kathryn T. Rimmer, Joshua Z. Willey, Kiran T. Thakur, Amelia K. Boehme, Wendy S. Vargas, Craig J. Smith, Mitchell S.V. Elkind

CDC Morbidity and Mortality Weekly Report (*MMWR*)
Weekly | July 31, 2020 | 69(30);993-998

Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network – United States, March-June 2020

COVID-19 sequelae may include persistent fatigue, cognitive dysfunction ("brain fog")

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https://www.paho.org/en/documents/epidemiological-alert-complications-and-sequelae-covid-19-12-august-2020
https://www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations--complications/post-covid-syndrome/
JAMA. 2020;324(6):603-605. doi:10.1001/jama.2020.12603
Journal of Medical Virology. https://doi.org/10.1002/jmv.26368
https://cp.neurology.org/content/early/2020/06/30/CPJ.0000000000000897

Summary

ME/CFS is a clinically and economically important disease

Diagnosis is based on history, exam and exclusion of other causes; nonetheless, there are biomarkers in many patients that suggest immunological, metabolic and microbiological abnormalities

Different phenotypes may indicate different causes and different strategies for intervention

There is symptom overlap with Gulf War Illness and possibly a post COVID-19 syndrome