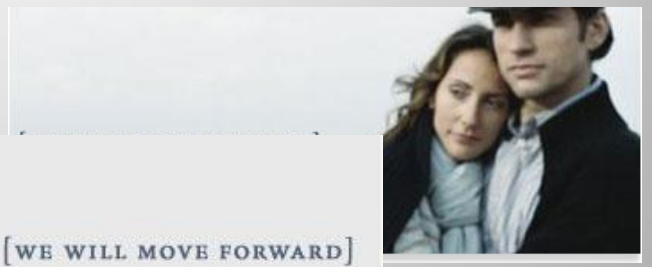

ME/ CFS

- Identifiable
- Treatable
- Fundable

Gordon Broderick, Ph.D.

Associate Professor, Dept. of Medicine,

University of Alberta

(Volunteer Associate Professor, Dept. of Medicine, University of Miami)

** CFIDS Association of America*

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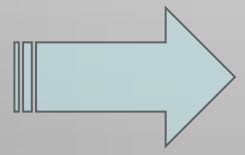
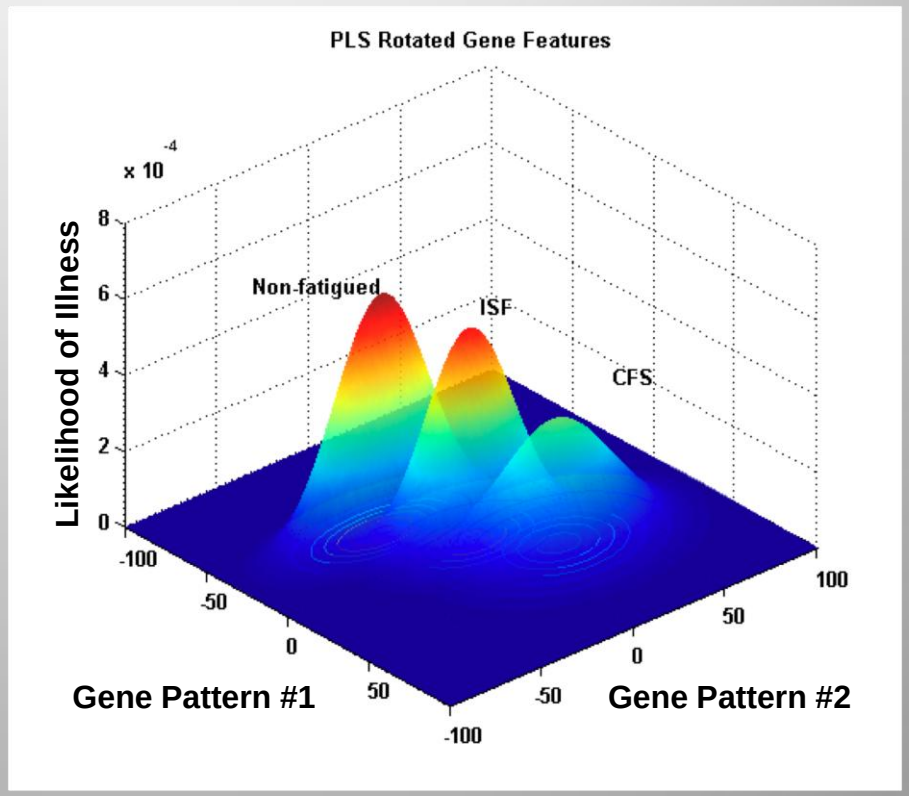
Identifiable: U.S. CDC Wichita Study

Clinical information (17% of 60 symptoms)





Gene expression (10% changes in 15,000 genes)

[1] Broderick et al., Identifying illness parameters in fatiguing syndromes using classical projection methods. Pharmacogenomics. 2006 Apr;7(3):407-19..

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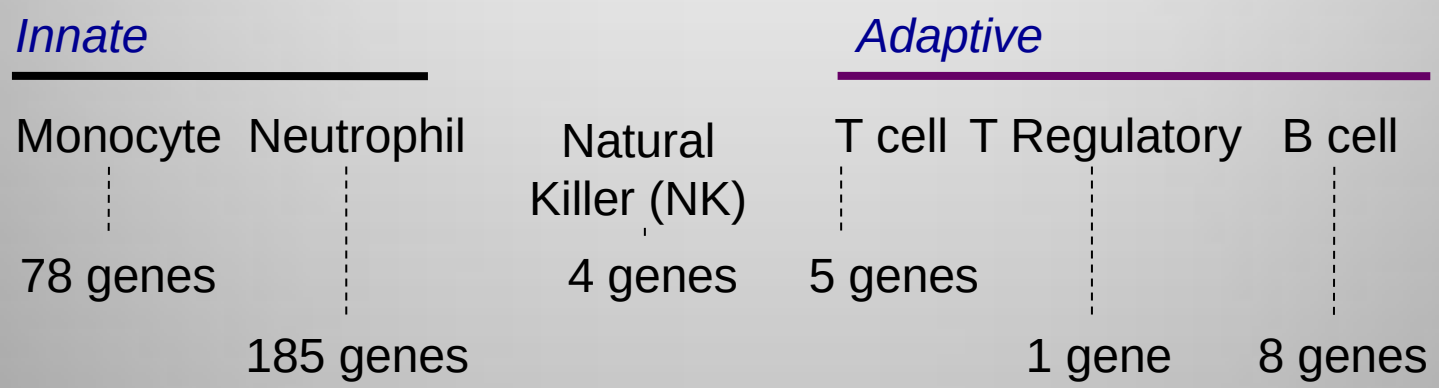
Identifiable: Inferring Immune Cell Activity

Identified genes better expressed in each of 6 cell types



- CFS subjects are *twice as likely to have low B cell gene activity (CD19+)*
- B lymphocytes known reservoir for latent EBV

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[1] Aspler AL, Bolshin C, Vernon SD, Broderick G. Evidence of inflammatory immune signaling in chronic fatigue syndrome: A pilot study of gene expression in peripheral blood. Behav Brain Funct. 2008 Sep 26;4:44.

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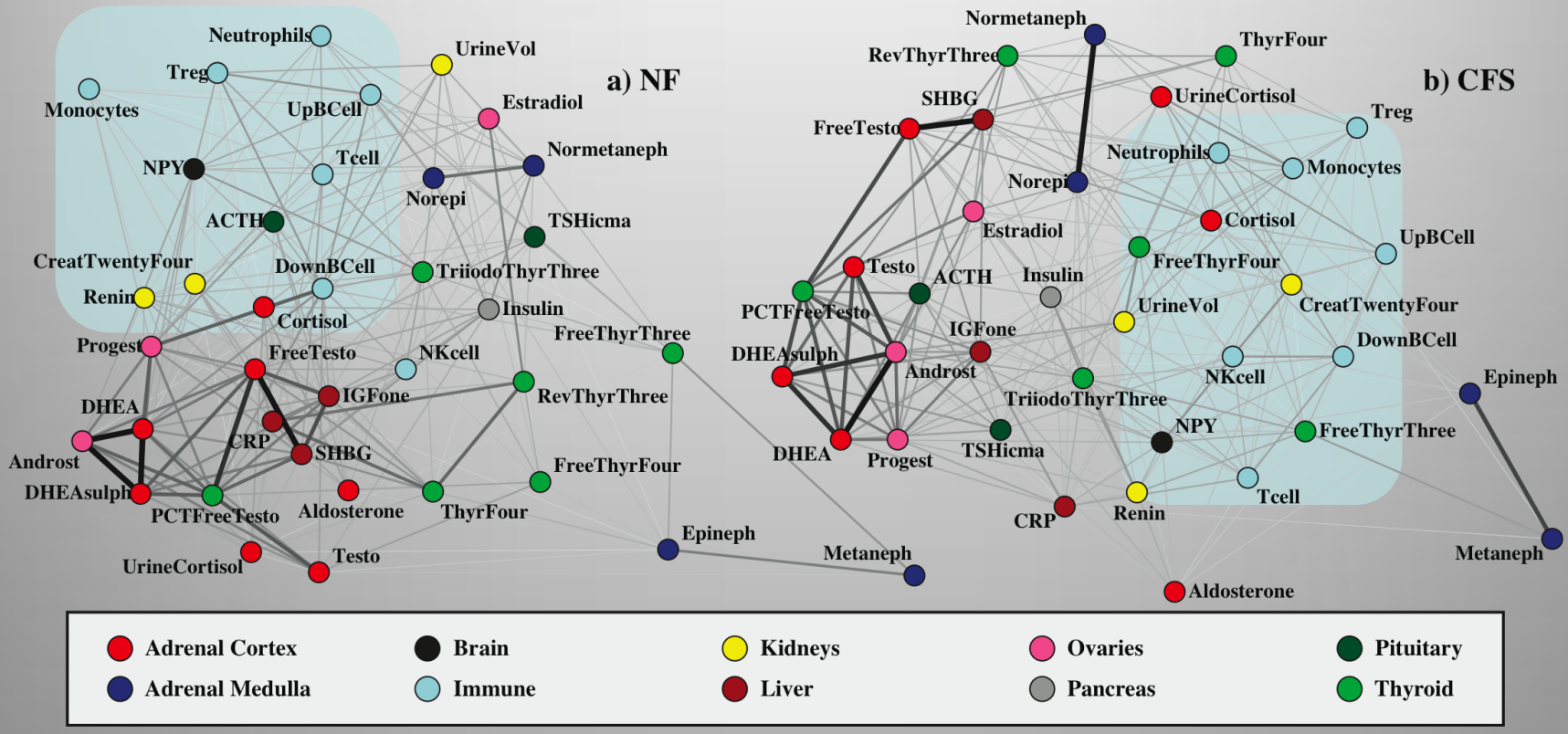
Identifiable: Looking at the Bigger Picture in Wichita

Immunity's ripple effect on 30 major hormones and neurotransmitters



[1] Fuite J, Vernon SD, Broderick G. Genomics. 2008 Dec;92(6):393-9. Epub 2008 Oct 1..

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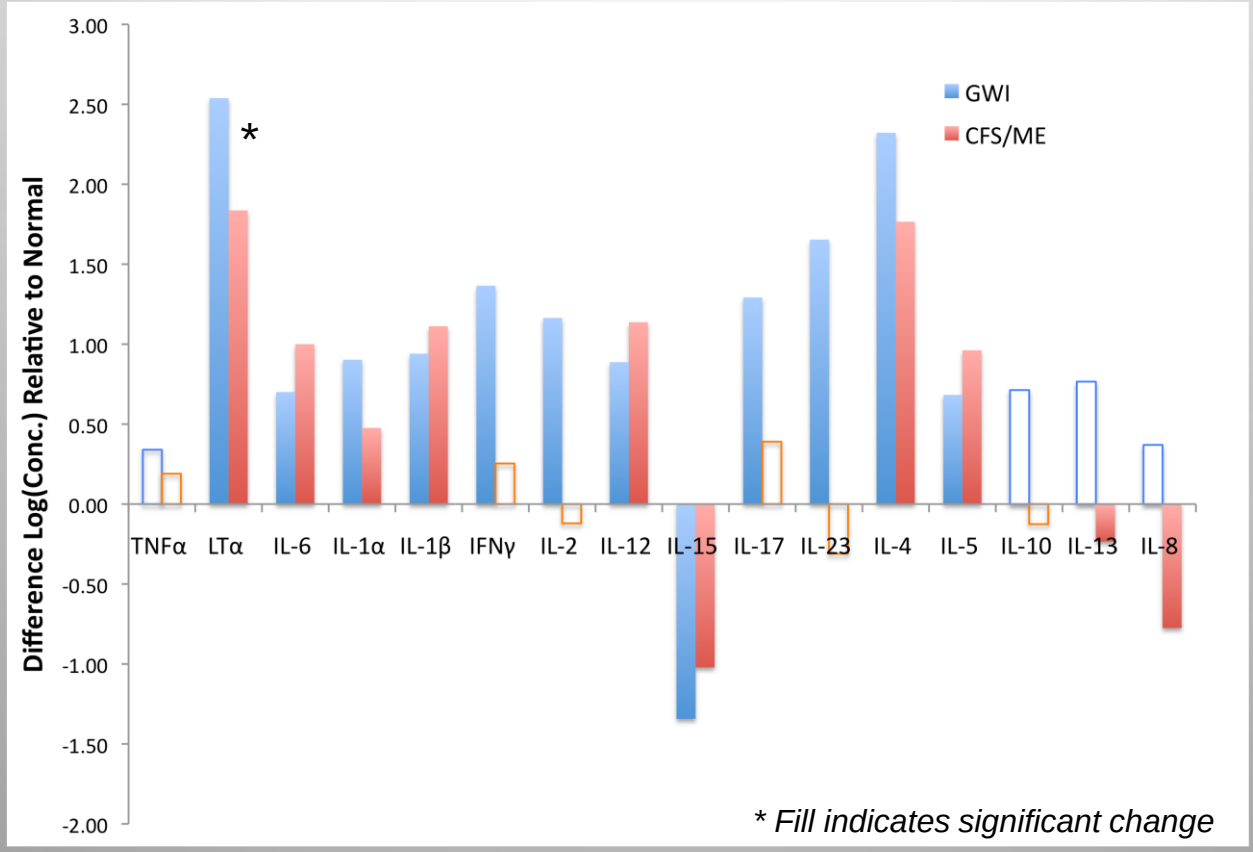
Identifiable: Broad and Significant Differences



- Significant changes across a broad range of immune markers in blood
- IFNg, IL-2, IL-17, IL-23 specific to GWI; IL-8, IL-13 *unique to CFS*

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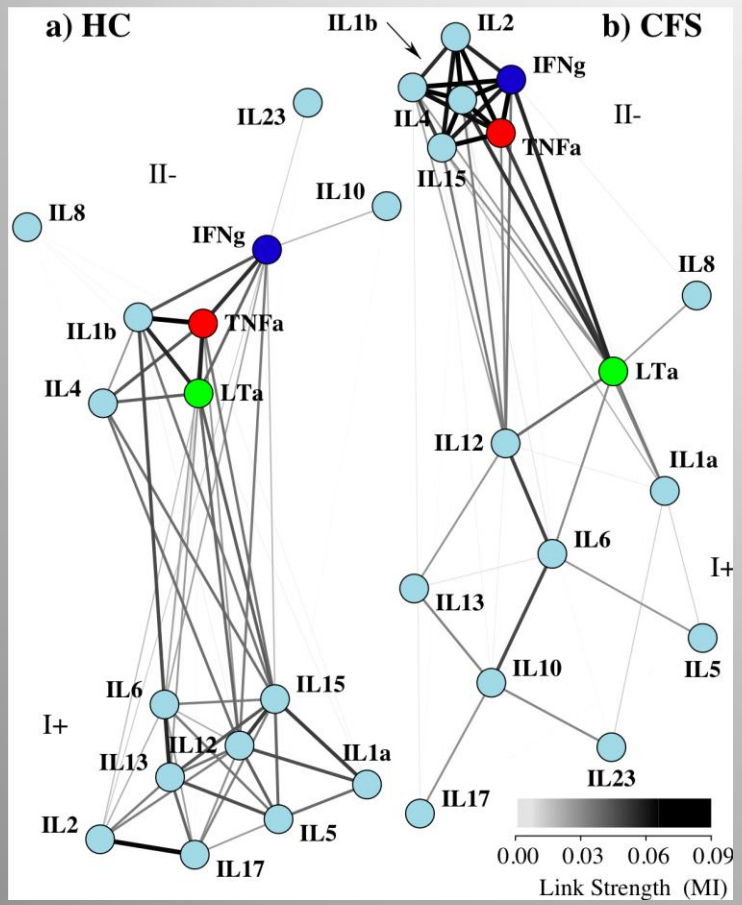
Identifiable: Patterns of Immune Activation [1]



Cohort of adult female CFS patients

- Immune network wiring looks different; *altered immune homeostasis*.
- Highly attenuated Th1 and Th17 responses.
- High Th2 expression and interactions pointed to allergic inflammation.
- Indirect evidence of diminished NK cell responsiveness to IL-12 and Lta .

Similarities *to latent viral infection…*

[1] Broderick G, et al.. A formal analysis of cytokine networks in Chronic Fatigue Syndrome. Brain Behav Immun. 2010 May 4

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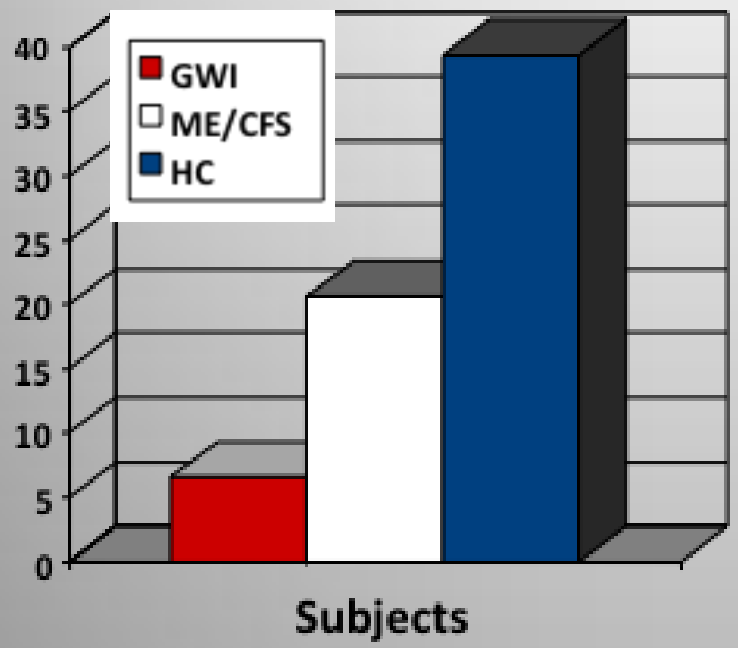
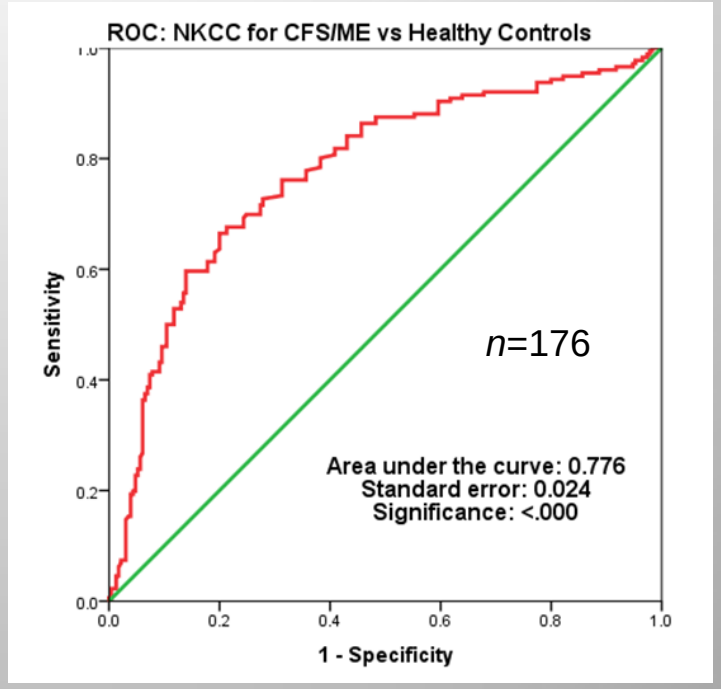
Identifiable: Broad and Significant Differences





- NK cell cytotoxicity significantly depressed in CFS/ME (also in GWI)
- Offers a credible mechanistic biomarker

Fletcher MA, et al. (2010) Biomarkers in Chronic Fatigue Syndrome: Evaluation of Natural Killer Cell Function and Dipeptidyl Peptidase IV/CD26. PLoS ONE 5(5): e10817. doi:10.1371/journal.pone.0010817

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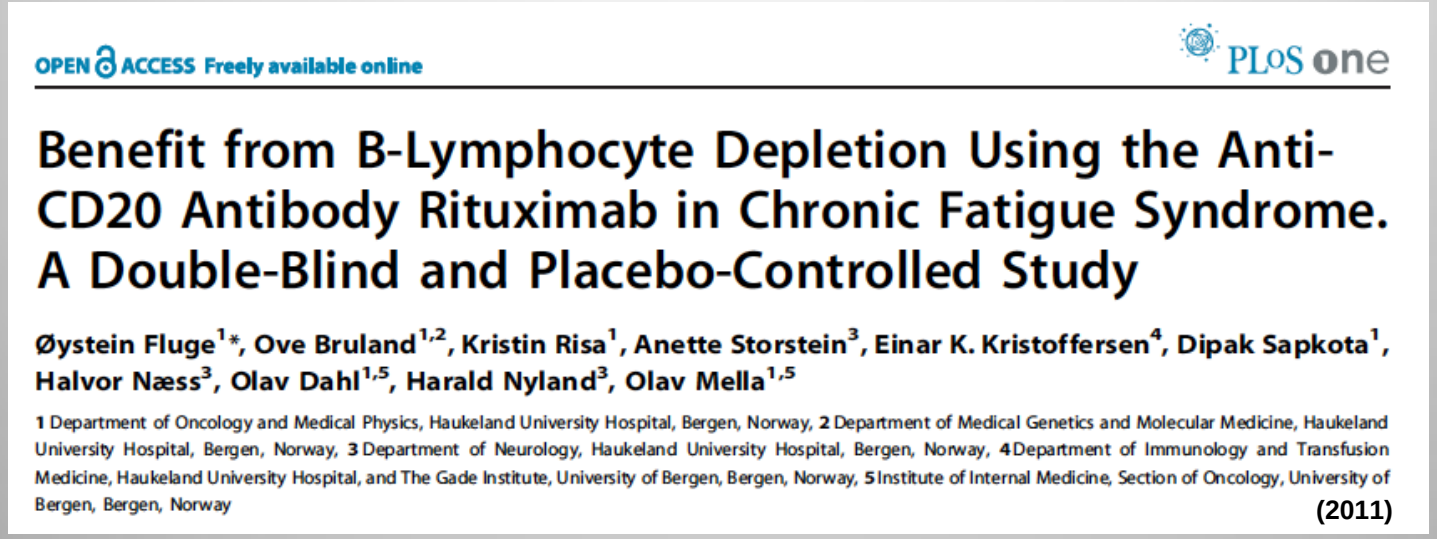
Treatable: Important precedents being set



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PLoS one

Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study

Øystein Fluge[1]*, Ove Bruland[1,2], Kristin Risa[1], Anette Storstein[3], Einar K. Kristoffersen[4], Dipak Sapkota[1], Halvor Næss[3], Olav Dahl[1,5], Harald Nyland[3], Olav Mella[1,5]

1 Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway, 2 Department of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway, 3 Department of Neurology, Haukeland University Hospital, Bergen, Norway, 4 Department of Immunology and Transfusion Medicine, Haukeland University Hospital, and The Gade Institute, University of Bergen, Bergen, Norway, 5 Institute of Internal Medicine, Section of Oncology, University of Bergen, Bergen, Norway

(2011)

Targeting B cells:

- Double-blind, placebo-controlled phase II study: n=30 CFS patients
- Randomised to Rituximab 500 mg/m2 or saline, twice two weeks apart, 12-month follow-up
- Reduced fatigue in 10 of 15 patients (67%) with Rituximab group vs. 2 of 15 patients (13%) with placebo (p = 0.003).

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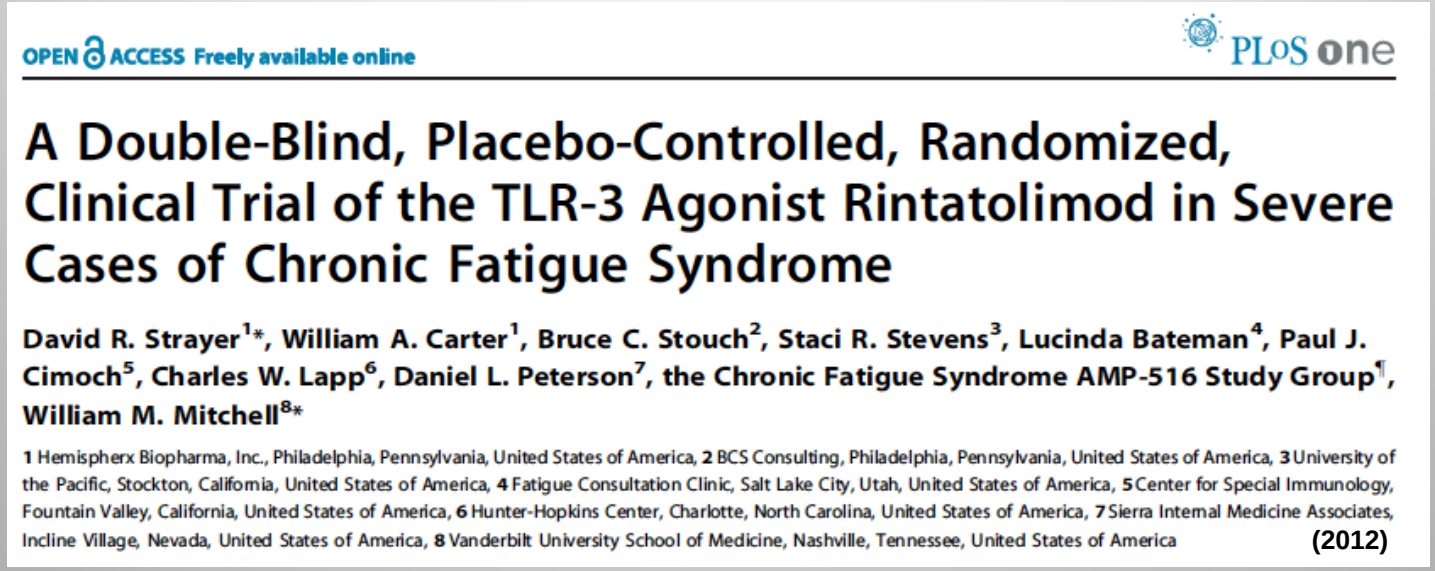
Treatable: Important precedents being set



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PLoS one

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

David R. Strayer[1]*, William A. Carter[1], Bruce C. Stouch[2], Staci R. Stevens[3], Lucinda Bateman[4], Paul J. Cimoch[5], Charles W. Lapp[6], Daniel L. Peterson[7], the Chronic Fatigue Syndrome AMP-516 Study Group[¶], William M. Mitchell[8]*

1 Hemispherx Biopharma, Inc., Philadelphia, Pennsylvania, United States of America, 2 BCS Consulting, Philadelphia, Pennsylvania, United States of America, 3 University of the Pacific, Stockton, California, United States of America, 4 Fatigue Consultation Clinic, Salt Lake City, Utah, United States of America, 5 Center for Special Immunology, Fountain Valley, California, United States of America, 6 Hunter-Hopkins Center, Charlotte, North Carolina, United States of America, 7 Sierra Internal Medicine Associates, Incline Village, Nevada, United States of America, 8 Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America

(2012)

Targeting NK cell function:

- Phase III multi-center (12), double-blind, placebo controlled: n=117 CFS patients
- Exercise tolerance (time to max exertion) as primary endpoint
- Randomised to 200 mg IV Rintatolimod or saline twice weekly,
- Improved exercise tolerance (>25%) in 1.9 times more frequent in treated subjects.

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Fundable: US NIH and DoD - A Recognised Public Health Issue

NIH has sponsored ME/CFS research awards since 1998 :

- R03 (2yrs; $100,000),
- R21 (2yrs; $275,000) and
- R01 (up to 5yrs; $500,000/yr) :

PATHOPHYSIOLOGY AND TREATMENT OF CHRONIC FATIGUE SYNDROME (CFS)

Re-issued based on NIH sponsored CFS science summit held in October 2000 at Arlington, VA

Current program due for review Nov. 2014

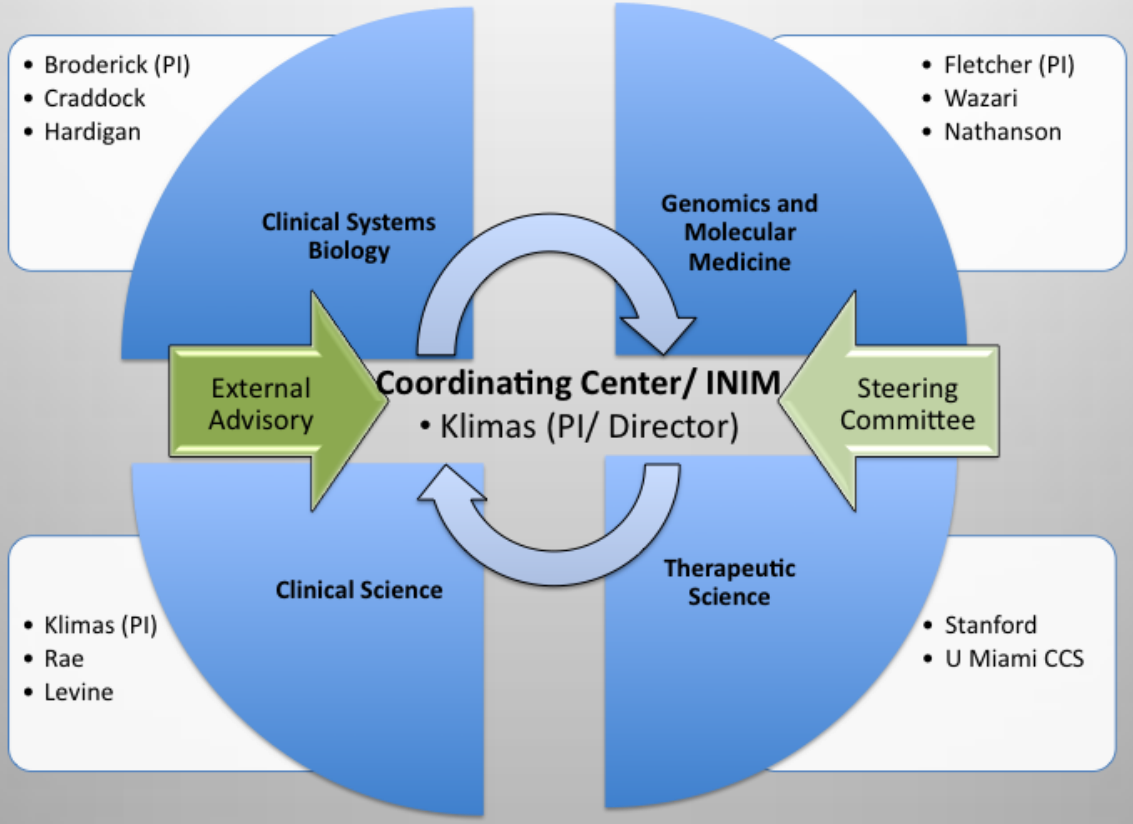
Fundable: US NIH and DoD - A Recognised Public Health Issue

Sponsored by among others:

- Office of Research on Women's Health (ORWH)
- National Institute of Allergy and Infectious Diseases (NIAID),
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS),
- National Institute for Diabetes and Digestive Diseases (NIDDK)
- National Institute of Neurological Disorders and Stroke (NINDS)

In 2011 the US DoD added ME/ CFS as a fundable topic to its Peer Reviewed Medical Research Program; $750,000 over 3 yrs

Critical Mass: A highly integrated, cross-disciplinary international team



- Focused effort building on strengths of 8 institutions (>$10 M effort)
- *Integrating* computer and experimental models with *in vitro* testing to design clinical treatment trials

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