Institute for Neuro-Immune Medicine

Nova Southeastern University Institute for Neuro-Immune Medicine

Institute mission statement

- To advance knowledge and care for people with complex
- neuro-inflammatory illnesses through research, clinical care and education

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Gulf War Illness

>25% of veterans returned from the first Gulf War Illness with a chronic often disabling multisymptom illness

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ME/Chronic Fatigue Syndrome

- **800,000 to 2.5 million Americans are affected with ME/CFS**
- **Five times more common in women**
- **Long-lasting, debilitating illness (heart disease, end stage renal, MS, AIDS)**
- **25% unemployed or receiving disability**

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NSU Institute for Neuro-Immune Medicine: Clinical Team

NSU/COM Institute in partnership with the Miami VAMC
Nancy Klimas, MD, Director
Nick Lewis, Institute Administrator
Irma Rey, MD Director, Medical Education
Maria Vera, MD Clinician
Lynn Lafferty, PharmD, ND , CNC, Integrative Medicine
Connie Sol, Exercise Physiologist
Irina Rosenfeld, ARNP, Phyllis Wagner, ARNP
Ernesto Martinez, MD Research Associate

NSU Institute for Neuro-Immune Medicine: Research Team

- Mariana Morris, PhD (Wright State)
- Gordon Broderick, PhD (Univ Alberta)
- Travis Craddock, PhD (Univ Alberta)
- Paula Waziry PhD (NSU)
- Lubov Nathanson, PhD (Univ of Miami)
- Maria Vera, MD (University of Miami)
- Mary Ann Fletcher, PhD (University of Miami)

Institute: Integrative Medicine with a Research Backbone

- Immunology
- Neuro-immunology
- Genomics
- Computational Biology
- Animal Modeling
- Biorepository Development
- Clinical Care
- Exercise physiology
- Nutrition
- Complementary Medicine

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Institute mission

- An integrated program, which will not separate the clinical, research, and education missions
- NSU investigators/clinicians/educators working through an international platform for collaboration with a wider network of institute fellows

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Institute mission

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- clinical care
- clinical research
- laboratory research
- computational research

Education , Research, Clinical Care

Finding New Interventions

Targeted therapies:

- improving cellular energy
- Enhancing antiviral functions
- Reducing neuroinflammation
- Reducing pain
- Quieting immune activation
- Enhancing adrenal function
- Correcting autonomic dysfunction

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Testing New Interventions

New strategies in design:

- RedCAP platform for assessment
- Nanostring platform, multiplex cytokines, immune function
- Dynamic Challenge to test response at clinical and biologic levels
- Computational biology / modeling analysis

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Treating Gulf War Illness
A Pathogenesis Based Approach

Nancy Klimas, MD
Nova Southeastern University and Miami VAMC

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Gulf War Illness	Chronic Fatigue Syndrome***
Fatigue	Disabling fatigue
Depression	Exercise induced relapse
Arthralgia	Arthralgia
Myalgia	Myalgia
Sleep disturbance	Non restorative sleep
Cognitive dysfunction	Cognitive dysfunction
Headache	Headache
Diarrhea, intermittent	Sore throat
Wheezing, **Cough,** **Chest pain,** **Shortness of breath***	Tender lymph nodes
Weight loss, low grade fever**	

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Model of Pathogenesis

Genetic Predisposition

↓

Triggering event / infection

↓

Mediators (Immune, endocrine, neuroendocrine, sleep, psychosocial, viral reactivation or persistence)

↓

GWI

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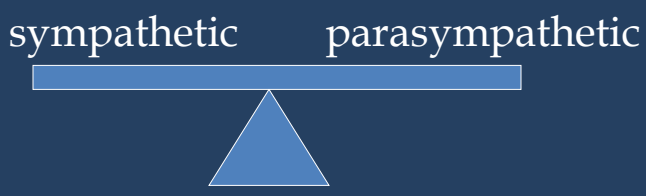
Autonomic Dysfunction

Neurally mediated hypotension (Rowe)
Orthostatic hypotension (Streeten)
Parasympathetic dysfunction (Sisto)
Sympathetic over activation (Pagini, De Becker)

Balancing Act



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Autonomic Nervous System

- Decreased cerebral perfusion at rest and after pyrostigmine challenge in GWI (Lui et al 2011)
- Haemodynamic Instability Score taken during tilt table testing predicts CFS with 90% sensitivity. (Naschitz et al 2003)
- Heart Rate variability as a predictor of CFS (Yamamoto et all 2003)
- HRV reduced in female GWI (Stein et al 2004)
- Gastric emptying delayed in 23/32 CFS subjects (Burnet et al 2004)

Autonomic Nervous System

- CFS/ME patients have a low blood volume state – nearly one liter lower than normal. Peckerman's GWI echo studies also suggests low volume state in GWI.
- In ME/CFS this reflects a matched RBC mass and plasma volume decrease, resulting in a misleading normal ratio, thus a normal CBC

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Implications for treatment - NMH

Remember: On a **good** day your patient is a liter short on blood volume

"Pipes and a pump", wired by the autonomic nervous system

- Fill the space – increase plasma volume (electrolyte or fludrocortisone)
- regulate the pump - beta blockers
- compress the space - alpha 1 agonists (e.g. midodrine),

  anti-phlebitic stockings, core muscle strengthening
- Reconditioning

Consider referral to cardiology or neurology for tilt table study

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Immune modulation in GWI

- Largely untested in GWI
- Evidence suggests two targets: reducing inflammation, particularly neuroinflammation and enhancing antiviral function, particularly cytotoxic function.

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Reducing inflammation

- *While biologic response modifiers are promising avenues for study there are some drugs and supplements that have been shown to quiet inflammation to some level in similar illnesses.*
- Omega 3 in high dosing ranges quiets TNF a ; low dose naltrexone to quiet neuro-inflammaotry pathways
- Reducing exposure to known immune stimulants such as allergens. Vaccine use has a different risk/benefit ratio than in healthy veterans and should be weighed based on past experience.

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Improving antiviral function

- Work up should include quantitative immunoglobulins, immunoglobulin subclasses. Our work also suggests cytotoxic functional assays are useful, and viral serologies.
- Enhancing cytotoxic function is a focus of our work. Supplements with palacebo control dat in related illnesses:
- inosine or isoprinosine,
- mushroom extracts,
- Equilibrant (Sophora root extract with immune modulatory effects).

Caution in the setting of autoimmune comorbid illness.

Viral Persistence/Reactivation

GWI: Increased titers to EBV6, HHV6, HSV, reduced T and NK cell function (Vojdani et al 2004, Klimas et al 2009)

CFS/ME:

HHV6 virus is present in 22 to 54% of patients in cross sectional studies (Ablashi, Krueger, Knox), HHV6 virus is present in 79% of CFS patients in longitudinal studies (HHV6 PCR assay, Knox)

HHV6 virus is present in the spinal fluid of 28 of 120 CFS patients (Peterson), and 7 of 35 CFS samples (Knox).

Enterovirus is present in 13% of CFS muscle samples (Douche-Aourik, 2003) 60% gastric biopies (Chia 2007)

EBV – dUTPase as a immune modulator, up regulating inflammatory cytokines (Glaser, 2005, 2012)

Antimicrobials

- No antiviral work done in GWI,
- mycoplasma study definitively negative

- In CFS/ME:
- Phase 1 study and a small phase 2 study of valgangcyclovir, in CFS patients with very high serology for EBV and HHV6 . In the phase 2 study improvement was seen in mental fatigue, note the need for high titer serology to predict response (Montoya et al)
- In vitro studies acyclovir derivative drugs have some anti-HHV6 effect at high dosage (e.g. acyclovir 800 tid)

HPA HPG HPT axis interventions: –

- Growth hormone studies in ME/CFS showed early promise, nothing similar in GWI
- Cortisol – conflicting phase 2 study results in ME/CFS(Cleare, Strauss) , Cleare notes responders showed normalization of DHEA, Leptin
- Estrogen , testosterone – normalizing hormone levels in low risk patients reasonable.
- Restoration of sleep cycle is not enough to correct HPA access dysregulation

Sleep Physiology

- Sleep disordered breathing in GWI – phase 1 of CPP promising
- In CFS/ME Circadian Sleep - Wake neuroendocrine and immune functions in CFS (Modolfsky)
- altered diurnal patterns in cortisol, prolactin
- altered diurnal patterns of NK cell function
- alpha wave intrusion on sleep EEG , reduced stage III (SWS)
- Higher %REM (Twin study, 22 discordant twins)[1]

1 Watson et al Sleep 2003 26(3):32-8

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Sleep: Treatment

•Re-establish circadian rhythm
•Consider CPAP for upper airway dysfunction

Conditioned response to bed - avoid bed for resting, reading, use bed for sleeping. Establish "bedtime".
• Avoid short acting hypnotics except in true insomnia (alpha trappers)
• tricyclics, doxepan are longer acting, and don't trap in alpha wave
• mirtazapine (Remeron), gamma hydroxybutyrate, (Xyrem) act as SWS inducers, ?melatonin,
•eszopiclone(Lunesta), zaleplon (Sonata), and zolpidem (Ambien) sleep neutral

•Sleep studies very helpful as many as 50% of profoundly fatigued people have sleep apnea

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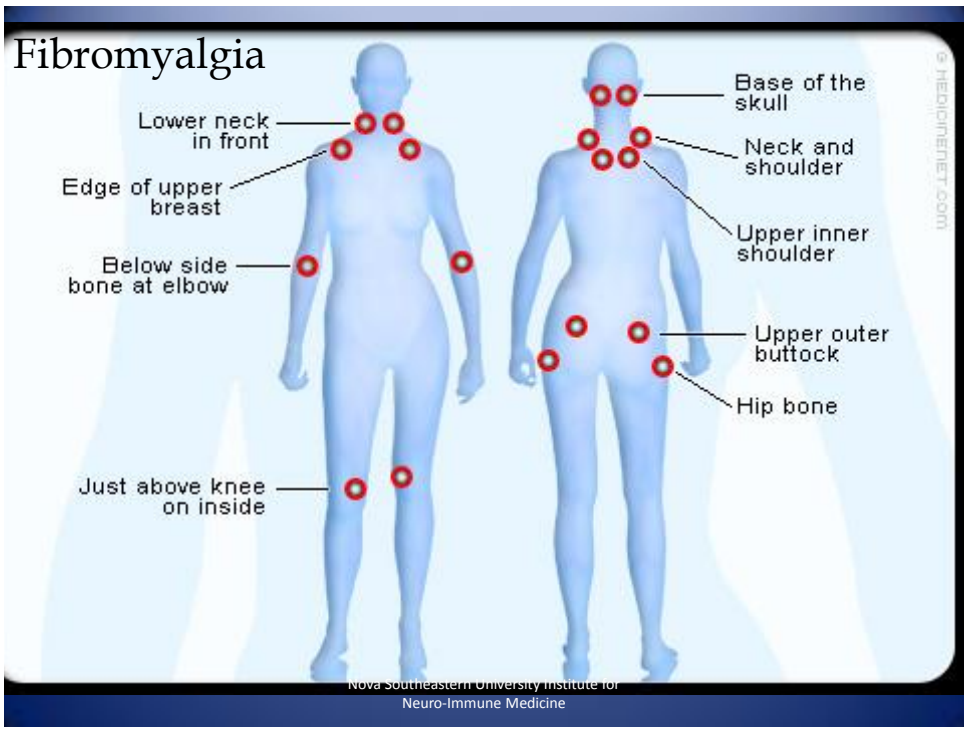
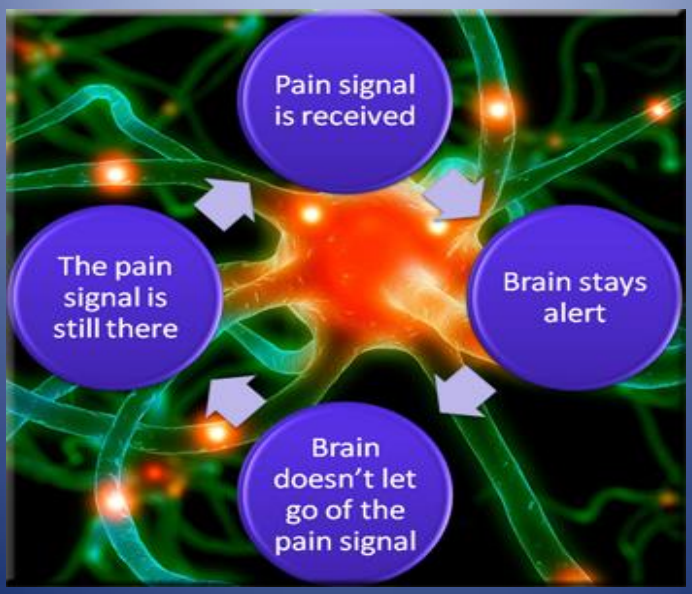
Pain and Sleep

Clinical dogma "restorative sleep is key to improvement"

The trials in FM report pain improvement with sleep restoration and vice versa

Experience has taught us that this is not always generalizable – it would be helpful if there were studies in GWI





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Pain

In Fibromyalgia patients and FM subset of GWI or CFS there are 3 labeled pain medications and 1 pipeline sleep medication

- Pregabulin (Lyrica)
- Duloxetine (Cymbalta)
- Milnacipran (Savella)

Finishing trials: sodium oxybate (Xyrem), low dose naltrexone (1.5 to 4.5 mg)

- Opiates, alcohol increase neuroinflammation and reinforce central pin processing upregulation

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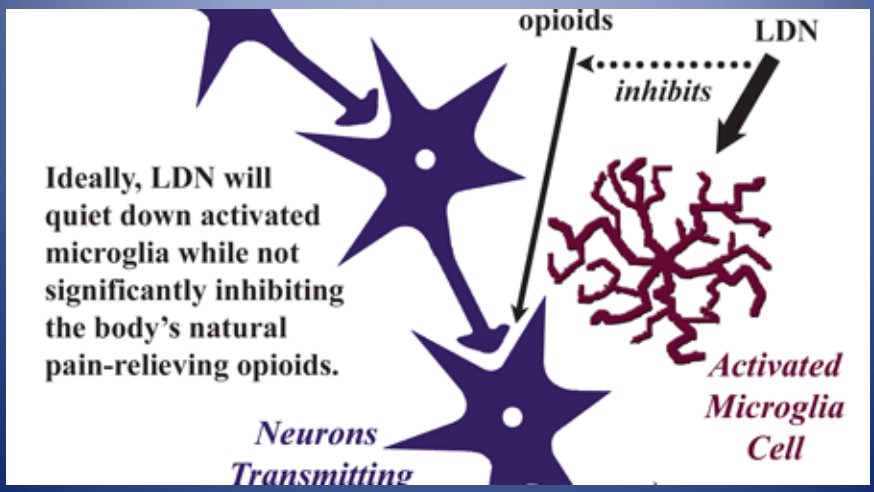
Low Dose Naltrexone



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Examples of MULTI-USE DRUGS	SLEEP	MH	PAIN	MIGRAINE	Side effects
TCA: amitriptyline, doxepin	+++	+	++	++	wt gain, OI, dry mouth
trazodone	++++	+			daytime sedation
SSRI : fluoxetine, sertraline, escitalopram mirtazapine	+/- +++	+++ + ++	+		daytime sedation
SNRI: venlafaxine duloxetine	+ +	+++ + +++	++ +++		weight loss
NSRI: Milnacipran	?	+	+++	?	nausea – take with food

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Examples of MULTI-USE DRUGS	SLEEP	MH	PAIN	MIGRAINE	OTHER
ACD anticonvulsants					
divalproex	++	+++	+	+++	hair loss some ACD's
gabapentin	+++	++	+++	+	weight gain
pregabalin	+++	+++	++++	+	brain fog
lamotrigine	+	++	+	+	brain fog, wt gain
topiramate	++	+	++	+++	rash
zonisamide	+/-	+/-	++	+	weight loss, brain fog
					weight loss
					sulfa allergy
ANTIPSYCHOTICS					
olanzapine (Zyprexa)	++++	+++			Weight gain
quetiapine (Seroquel)	+++	+++			Weight gain

Nutritional interventions

Dangers:

- Licorice root – potassium deficiencies
- "supplements" that are actually hormones
- "supplements" that have iffy contents – eg. St John's wort, melatonin
- Products that make unsubstantiated claims
- Under and over hydration

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Nutritional interventions

- Oxidative stress studies suggest interventions such as glutathione, N-acytylcysteine, alpha lipoic acid, NADH
- Vitamin studies suggest B vitamins, Vitamin C, magnesium, sodium, zinc, l-tryptophan, L carnitine, co-Q10, and essential fatty acids
- CoQ 10 is the only medication with favorable GWI data in palcebo control studies
- highlighted interventions have randomized clinical trials published

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CoQ10 and GWI

- Placebo control studies at 100 bid and 300 bid
- 100 bid showed efficacy
- 300 bid lost the presumed benefit due to hs dosing acitvating and reducing quality of sleep

- So - don't take coq10 at bedtime
- Ubiquinol 100 bid or ubiquinone 300 bid

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Nutritional interventions

- Vitamin D optimized to a level of 60 or greater
- Omega 3 fatty acids (fish oil, flaxseed) 2000 mg bid
- Sublingual B complex daily
- Ubiquinol 100 mg BID or 200 q am

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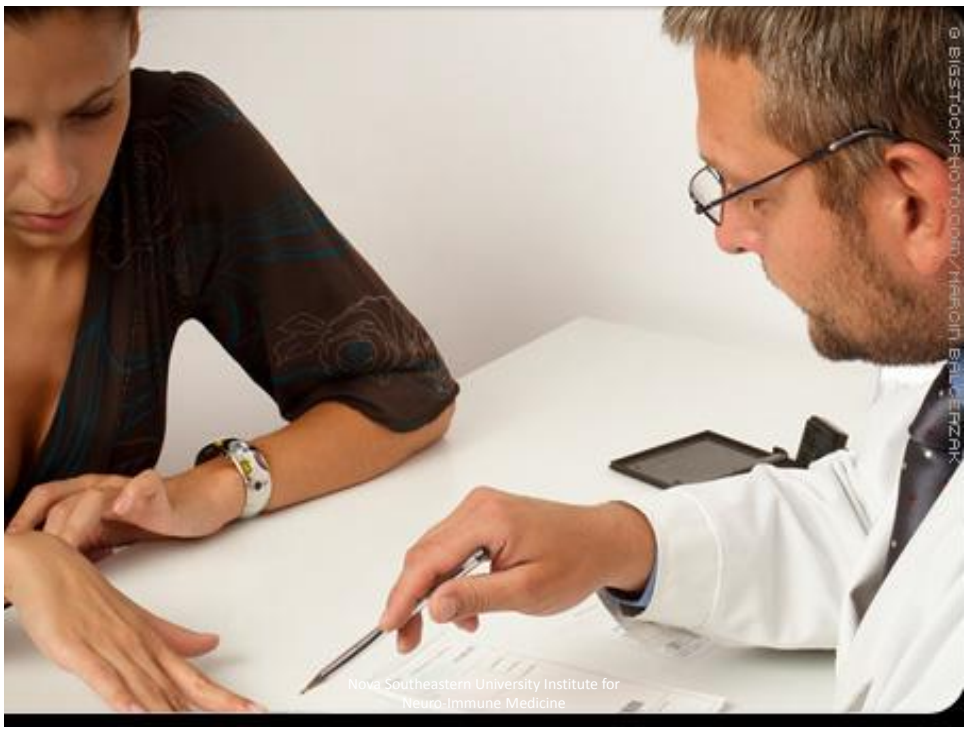
Reconditioning/ CBT

Poor orthostatic resilience leads to substantial challenges to usual reconditioning programs

- Concentrate on muscle bulking exercises, increasing metabolic rate (weight training, light weights)
- Flexibility , stretching and balance as core component.
- When possible obtain VO2 max and use pulse meter to keep effort below areobic threshold
- If not, then limit upright head up time to 5 minutes aerobic alternating with 10 minutes flat rest, use flat or near flat aerobic conditions (swimming, recumbent bike)



Conclusion

- GW era vets are at high risk for GWI and CFS/ME like illness
- There has been significant progress in our understanding of GWI and CFS/ME.
- The neuroendocrine, immune, and central nervous system are linked, and can't be considered separately. Seeing the illness as a homeostasis reset has important treatment implications.
- Subgroups, including virally infected patients suggest targeting therapies.
- More effective therapies, based on this new understanding are available, with others under study.

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Practical Implications based on our groups work thus far

Medications directed at reducing inflammation, and oxidative stress, particularly neuroinflammation - e.g. low dose naltrexone (Dr Meggs recruiting), high dose omega 3 fatty acids, antioxidants, e.g. CoQ 10 (work of Beatrice Golumb et al)

Avoidance of toxins particularly naphthalene, petroleum product derivatives based on abnormal detoxification pathways

Repeated stress responses help to potentiate the illness, buffering stress makes a difference (e.g. CBT)

Exercise intolerance is very real and exercising to VO2 max will cause relapse. Working within an "energy envelop" can be helpful – we use pulse alarms set below VO2 max.

Optimize cellular energy/repair mechanisms – measure and optimize vitamin D, B12. work on nutrition and judicious use of supplements

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Primary care, GWI and VA resources

- Without an "expert" GWI clinic, care is still accessible in the VA
- PCP to manage endocrine, pain, sleep
- Sleep clinic to rule out apnea and assist in restorative sleep
- Rehab/PT/chiropractic/acupuncture to helpwith pain management and develop rehab program. MOVE would need adaptation to the limits of the illness
- Cardiology for autonomic dysfunction if needed
- Endocrine for complex endocrine management, metabolic disorder
- Comorbid conditions management as needed ; watch for PTSD and situational depression

Part 3

- **Are men and women different? Does it matter?**

Are men and women different? Does it matter?

- Although men with GWI have been extensively studied, we know less about women veterans with GWI due to the limited numbers of female veterans in pathogenesis studies.
- Large survey studies, particularly those evaluating fertility and risk of birth defects have revealed inconclusive results per OIM Reports (OIM, 2009).
- However, a few studies assessing gender differences have revealed that women appear to present with increased autonomic abnormalities, as measured by heart rate variability (Stein et al 2004) some differences in symptom cluster (Kang et al 2005), as compared to their male counterparts.

Neuroendocrine, Autonomic, Immune interactions in GWI and CFS/ME: Implications for Women

- Previous research efforts revealed that endocrine, autonomic and immune abnormalities were more prevalent in GW deployed veterans as compared to HC.
- These systems co-regulate each other, and dysregulation in one system will impact the others

Hormone	Examples of Immune Cells with Receptors
Gluccocorticoids	T and B-lymphocytes, neutrophils, monocytes/macrophages
Substance P	T and B-lymphocytes, eosinophils, mast cells, monocytes/macrophages
Neuropeptide Y	T-lymphocytes, monocytes/macrophages
Corticotropin Releasing Hormone	T and B-lymphocytes, mast cells, monocytes/macrophages
Prolactin	T and B-lymphocytes, granulocytes, precursor cells, monocytes/macrophages
Growth Hormone	T and B-lymphocytes, monocytes/macrophages
Catecholamines (epinephrine/norepinephrine)	T and B-lymphocytes, neutrophils, NK cells, monocytes/macrophages
Serotonin	T and B-lymphocytes, NK cells, monocytes/macrophages

Glaser and Kiecolt-Glaser, *Nature Reviews Immunology*, 2005

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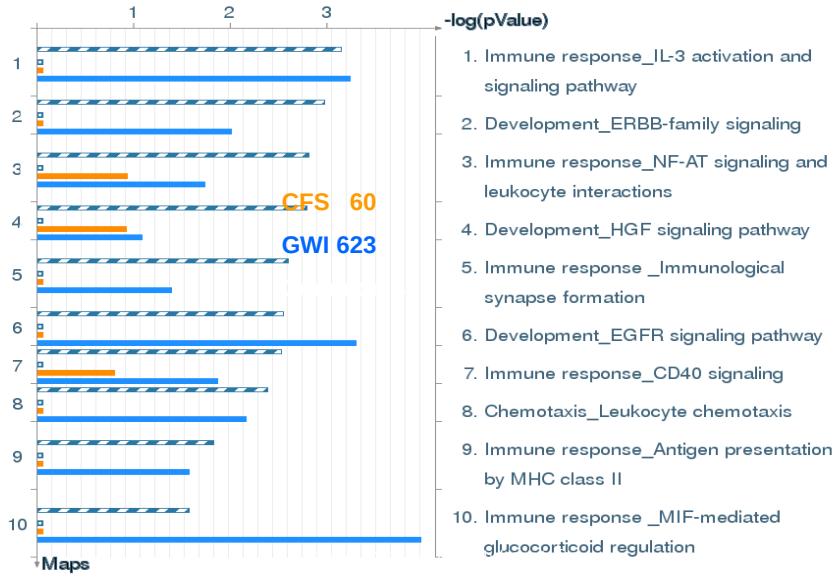
From 650 potential pathways



Top Gene Go Processes GWI T0T2

4 hours post exercise: GWI	value
regulation of multicellular organismal process	5.082e-11
negative regulation of blood pressure	3.656e-10
regulation of sensory perception of pain	3.640e-09
regulation of sensory perception	3.640e-09
positive regulation of nitric oxide biosynthetic process	3.115e-08
positive regulation of nitrogen compound metabolic process	4.041e-08
response to stress	6.203e-08
regulation of developmental process	6.445e-08
regulation of nitric oxide biosynthetic process	8.186e-08
regulation of blood pressure	9.707e-08

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GWI and CFS : Comparisons

- Both defined by symptoms which overlap
- Significant overlap in research findings
- Study of GW veterans showed a 16 fold increase risk of CFS, but no other increased risk over controls
- Issues surrounding the study of a multi-symptom illness with a multisystem pathogenesis are the same

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Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis

- HPA dysregulation has been implicated in the pathophysiology of GWI (Golier et al., 2006; 2007; Unwin et al., 1999) and CFS/ME (Crofford et al., 2004), with potential different regulatory mechanisms between genders, though insufficient numbers of women having been studied.
- The influence of sex hormones on these findings has yet to be determined.

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Dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis

- Steroid hormones are generally implicated in the immune response, with estrogens serving as enhancers, at least, of the humoral immunity and androgens and progesterone (and glucocorticoids) as natural immunosuppressors. (Cutilo, review 2004).
- Sexual dimorphism in human immune systems is most apparent in the female predominance of certain autoimmune diseases (ADs) like systemic lupus erythematosus and rheumatoid arthritis.

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Discordant models – male and female predominance

- In our modeling studies, the male GWI model there is up regulation of signaling pathways, and traffic through the sex hormone nodes.
- These impact immune and cellular pathways
- In the predominantly female CFS/ME model quite the opposite is true, signaling is reduced or shut down and the is a down regulation of signaling and metabolic pathways, again trafficking through sex hormone nodes in a regulatory network that can be clearly defined.

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HPA HPT and HPG axis and immune regulation

- HPA influences immune function in well recognized ways: cortisol regulation, thyroid mediated metabolic dysfunction and through regulatory networks, autonomic and immune function.

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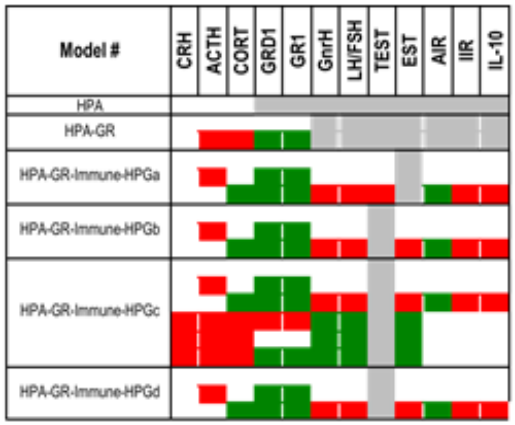
Gender and steady states



Gupta-Aslakson et al., 2007.

Male
hypercortisolic

Positive HPG feedback, mutually inhibitory with HPA = hypocortisolic

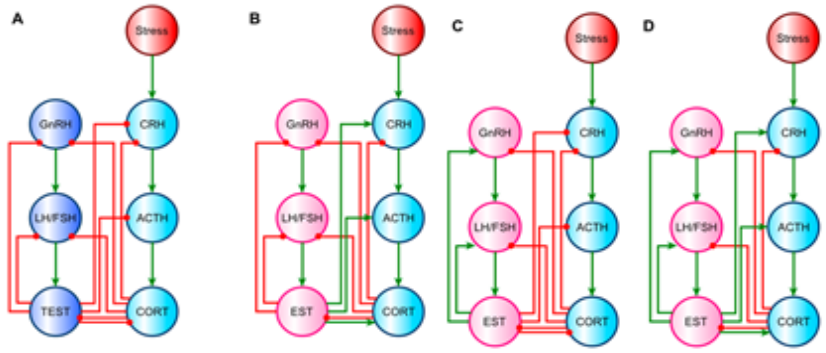
Female

- Gender effects have a major impact on available steady states…

Sex hormone regulation and Healthy Individuals

Male HPA-HPG-Immune model (a)

Female HPA-HPG-Immune model (b, c and d)



- Male HPG axis typically inhibits HPA activity; *a little more complex in women…*

Cytokines, disease and gender: GWI

- Initially the literature suggested a Th-2 shift (Rook and Zumla (1997) though later work suggested a mixed abnormal cytokine pattern involving bothTh1 and Th2 cytokines. Zhang et al. (1999), Skowera et al. (2004) , Allen et al. (2006) , Peakman et al., (2006)
- Brimacombe et al. (2002) concluded that while Th-1 markers described CFS/ME status in GW veterans, a Th-2 response factor produces exerts an effect on cognitive function in this population.
- A mixed Th-1: Th-2 immune status is also consistent with our recent work in a small cohort of male subjects (n=11, age 43 ± 2.1 years [30-55 years]) where we found higher response to PHA stimulation in GWI subjects for TNF-α at rest as well as in IL-5 and IFN-γ during the course of a maximal exercise challenge (Broderick et al., 2011).

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Th17 and GWI

- **Described in 2007, T helper 17 cells** (**T_h17**) are a subset of T helper cells producing IL17. They are developmentally distinct from Th1 and Th2 cells.
- They create inflammation and tissue in autoimmune disease such as multiple sclerosis, autoimmune uveitis, juvenile diabetes, rheumatoid arthritis, and Crohn's disease.
- Their normal role is to provide anti-microbial immunity at the epithelial/mucosal barriers.

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A comparison of sex-specific immune signatures in Gulf War illness and chronic fatigue syndrome

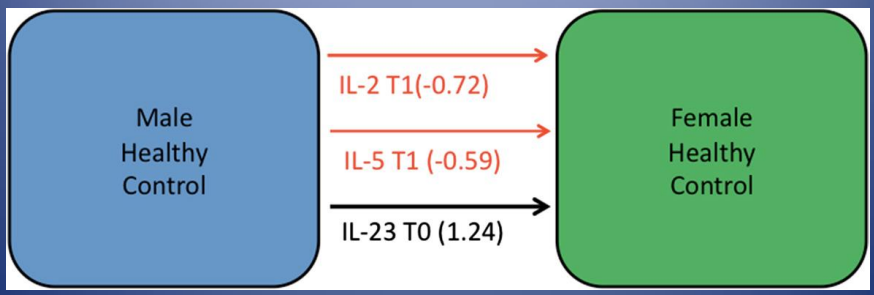
Anne Liese Smylie, Gordon Broderick, Henrique Fernandes, Shirin Razdan, Zachary Barnes, Fanny Collado, Connie Sol, Mary Ann Fletcher, and Nancy Klimas

BMC Immunol. 2013; 14: 29; June 25,2013

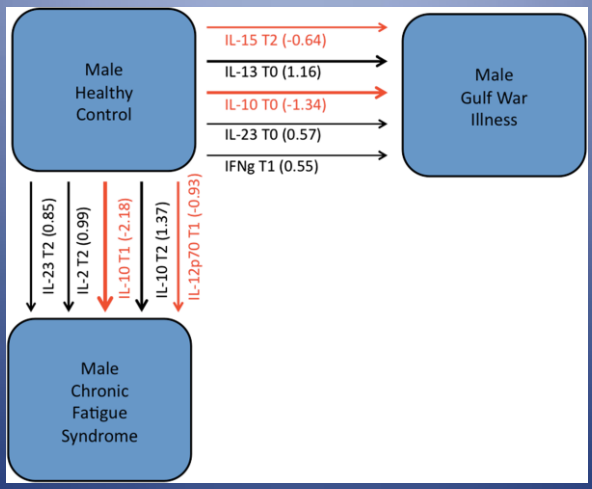
Method:

- Subjects were assessed using a Graded eXercise Test (GXT) with blood drawn prior to exercise, at peak effort (VO2 max) and 4-hours post exercise.
- Using chemiluminescent imaging we measured the concentrations of
- IL-1a, 1b, 2, 4, 5, 6, 8, 10, 12 (p70), 13, 15, 17 and 23, IFN**γ**, TNF**α** and TNF**β** in plasma samples from each phase of exercise.
- Linear classification models were constructed using stepwise variable selection to identify cytokine co-expression patterns characteristic of each subject group.

Gender differences, Healthy controls



Male Gulf War and Male ME/CFS



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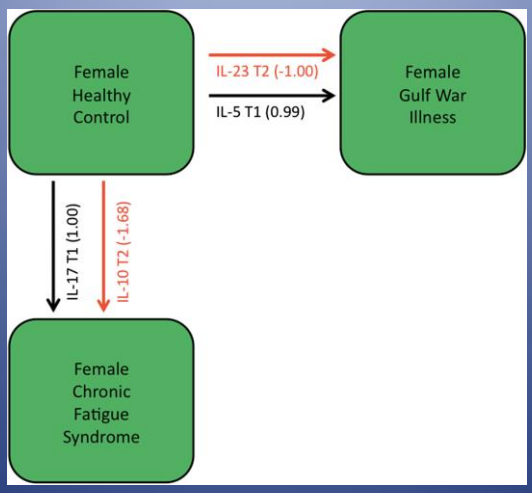
Female GWI and Female ME/CFS



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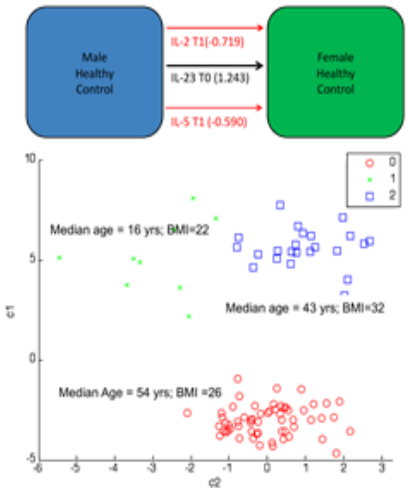
Alignment with Experimental Data



Healthy baseline: a gender-based moving target

- Cytokines separate men and women
- In women: very significant pre, peri and post-menopausal effects.

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GWI, Gender and Cytokines: conclusions

- In both GWI and ME/CFS IL-10 and IL-23 expression contribute to illness in a time-dependent manner, accompanied in male subjects by NK and Th1 markers IL-12, IL-15, IL-2 and IFNγ.
- In female GWI and ME/CFS subjects IL-10 was again identified as a delineator but this time in the context of IL-17 and Th2 markers IL-4 and IL-5.
- Exercise response also differed between sexes: male GWI subjects presented characteristic cytokine signatures at rest but not at peak effort , the opposite was true for female subjects.
- Conclusions: Though individual markers varied, results collectively supported involvement of the IL-23/Th17/IL-17 axis in the delineation of GWI and ME/CFS in a sex-specific way.

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Women, Men, GWI and ME/CFS

- The results suggest that GWI and CFS/ME are mediated differently, and the mediators of relapse and persistence in women with GWI are different than those in men.
- Currently this is in cytokine networks only, additional GWI female subjects are necessary to allow adequate power for the genomic analysis and networking analyses necessary to model and locate therapeutic targets.

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The Nation's Medical Research Agency

CFIDS Association of America
working to conquer chronic fatigue and immune dysfunction syndrome