

# ALTERED IMMUNE FUNCTION IN GWI AND POTENTIAL THERAPIES

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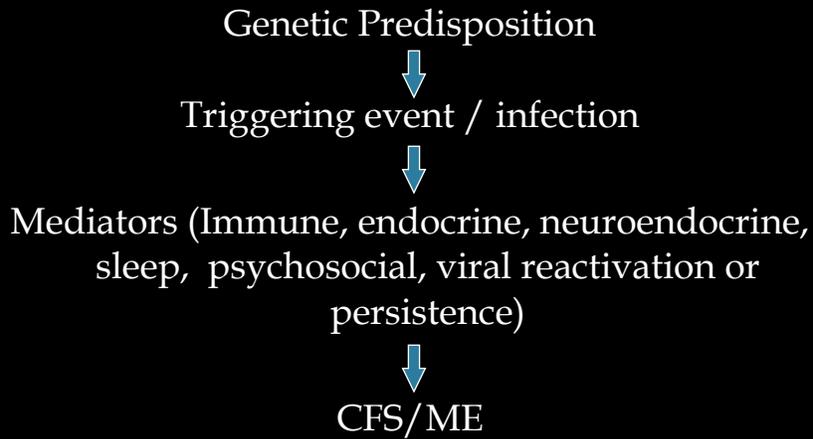


University of Miami/Miami VAMC CFS and GWI  
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# MODEL OF PATHOGENESIS



Hormone	Examples of Immune Cells with Receptors
Glucocorticoids	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

## Mediators

- ❑ The interaction between mediators is key
- ❑ We approach CFS as an illness with a homeostasis “reset” the new homeostasis set point maintains disruptions of immune, endocrine and autonomic interaction
- ❑ The immune, autonomic, and endocrine systems find a new balance and promote symptoms
- ❑ Chronic immune activation is a key component of this model.

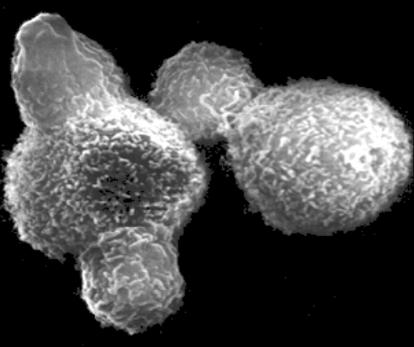
## Immune abnormalities in GWI

### Immune Activation

- ❑ DR, CD26, CD 38 expression
- ❑ TH2 cytokine shift
- ❑ Proinflammatory cytokines expression  
TNF- $\alpha$ , IL-1, IL6

### Functional defects

- NK Cell dysfunction
- CD8 abnormalities  
↓ perforins, granzymes
- Macrophage abnormalities
- Antibody production



NK cells and cytotoxic T cells function in a similar way - recognizing a cell, attaching, delivering cytolytic enzymes, releasing and moving to a new target.

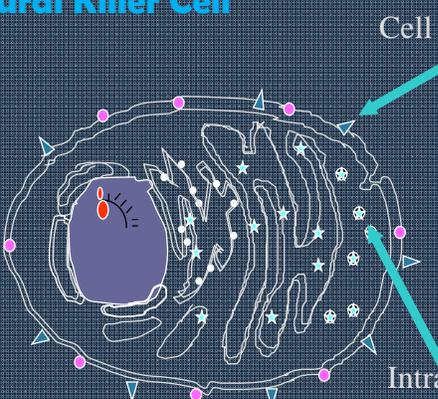
The difference is in cell recognition: the More primitive NK cells look for "non-self"; Cytotoxic T cells clone and create large Numbers of antigen specific cells.

They are both functioning poorly in GWI



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### Natural Killer Cell

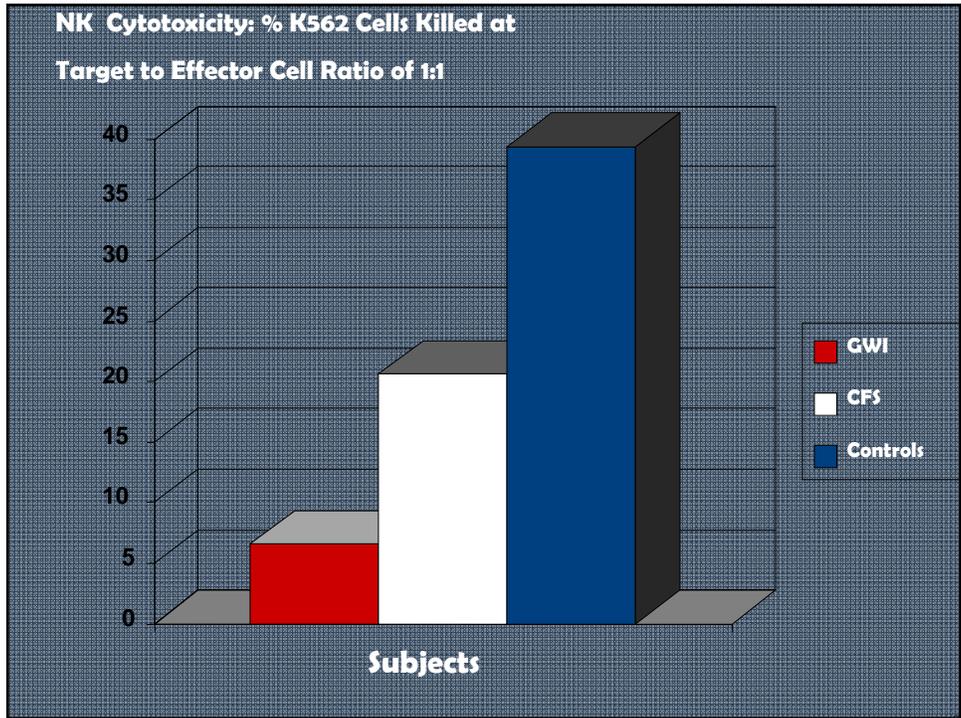


Cell Surface Antigen: CD56

Intracellular Cytolytic Granules:

- \* Perforin
- \* Granzyme A
- \* Granzyme B

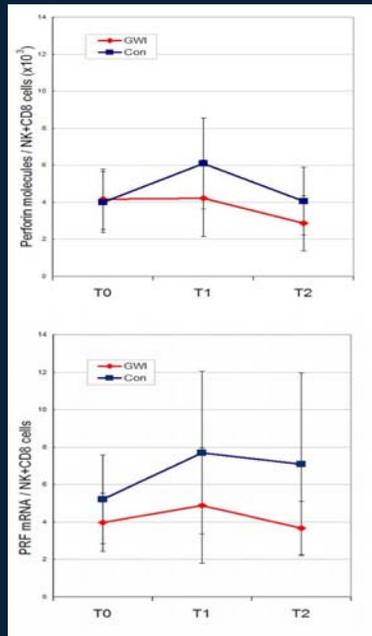
**Perforin is a molecule in cytotoxic lymphocytes necessary for killing of virus infected and tumor cells.**

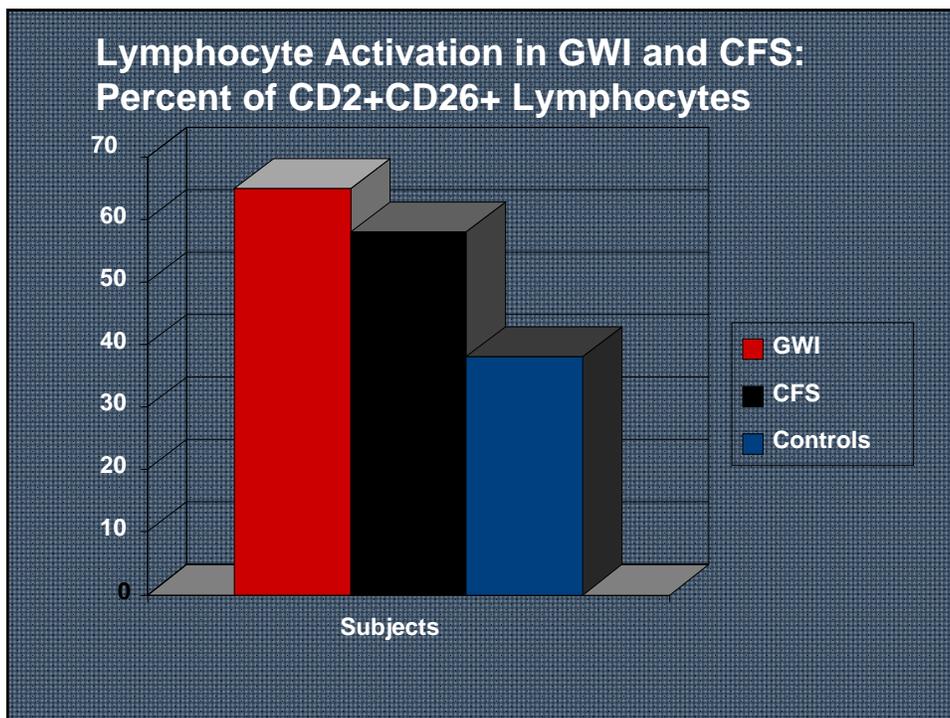
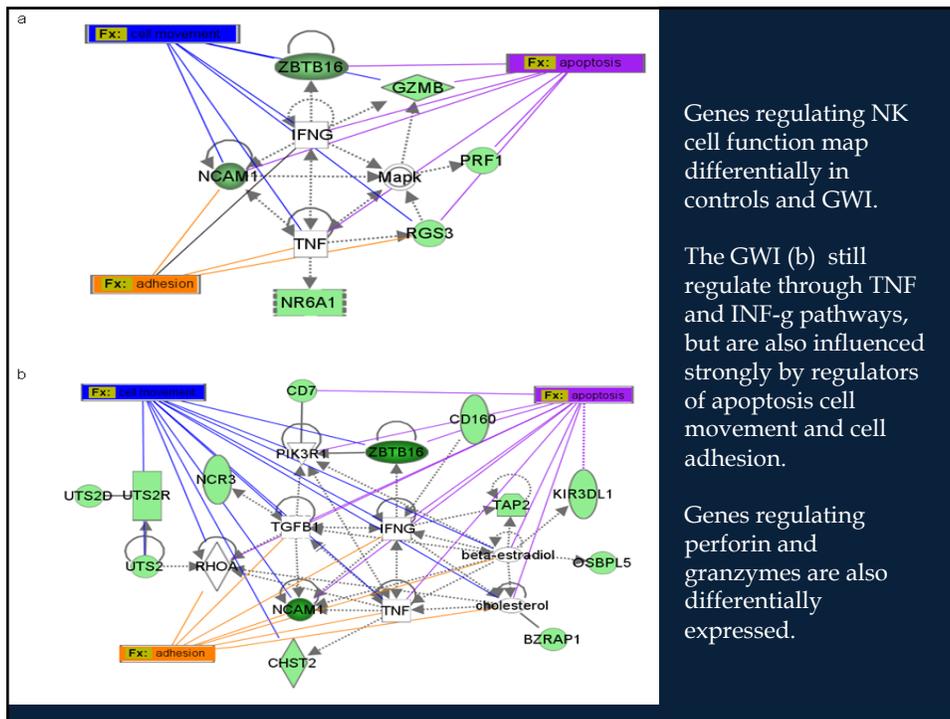


Change in perforin levels during an exercise challenge time series adjusted for the number of **NK** and **CD8+** cells.

The top graph shows intracellular perforin molecules in both **NK** and **CD8 T-cells** and the bottom graph the gene expression data (mean signal intensity).

BMC Med Genomics. 2009; 2: 12. Published online 2009 March 5. Impaired immune function in Gulf War Illness Toni Whistler, Mary Ann Fletcher, William Lonergan, Xiao-R Zeng, Jin-Mann Lin, Arthur LaPerriere, Suzanne D Vernon, Nancy G Klimas

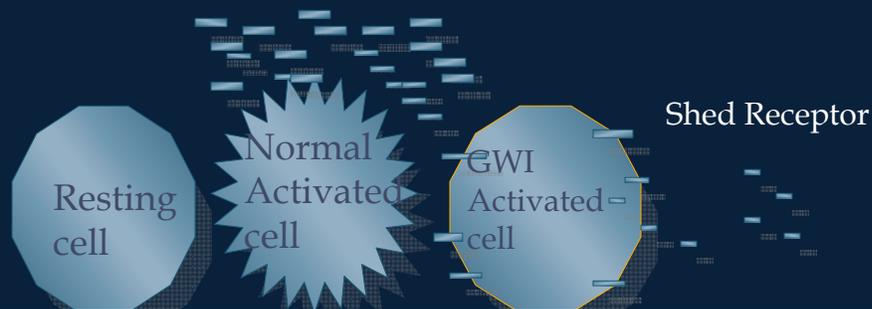




**CD26 (dipeptidyl peptidase IV) is involved in the activation of T cells, and is expressed on antigen-reactive memory T cells.**

**As reported by our research group, the percentage and number of CD26+ lymphocytes is elevated in CFS and GWI.**

Quantification of CD26 per cell is reduced in both conditions.



**Neuropeptide-Y (NPY) helps to regulate of a large number of physiological and pathophysiological processes.**

**cardiorespiratory system**

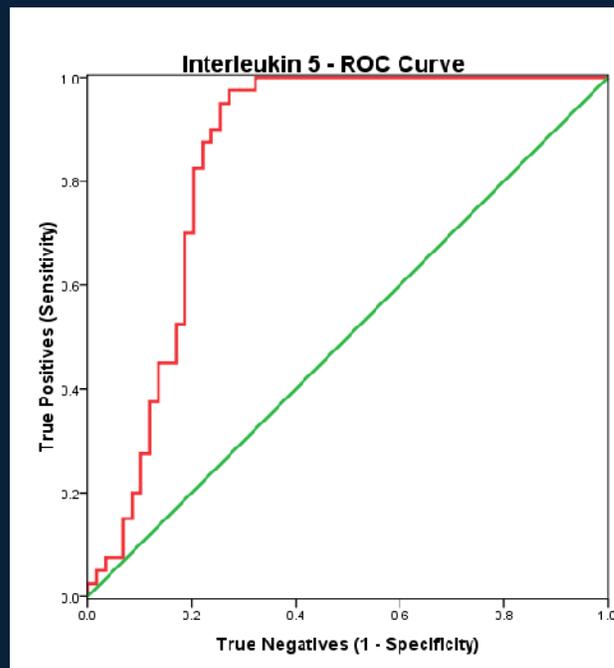
**immune system**

**nervous system**

**endocrine system**

<b>Signal molecules Plasma levels</b>	<b>Ctrl</b>	<b>GWI</b>	<b>EGWI - Ectrl</b>	<b>P value</b>
IL-6	12.60 (0.76)	3.45 (0.23)	9.15	0.00
IL-10	10.07 (0.85)	3.78 (0.19)	6.29	0.00
TNF-a	0.05 (0.00)	4.89 (0.19)	4.84	0.00
SCD26	2.13 (0.08)	6.94 (0.53)	4.81	0.00
NPY	7.71 (0.55)	12.23 (0.84)	4.52	0.00

<b>PHA-stimulated blood culture</b>	<b>Ctrl</b>	<b>GWI</b>	<b>EGWI - Ectrl</b>	<b>P value</b>
Saliva Cortisol	3.12 (0.15)	6.10 (0.32)	2.98	0.00
IL-1a	2.12 (0.12)	22.01 (1.68)	19.89	0.00
IL-5	3.39 (0.28)	13.06 (0.45)	9.67	0.00
IL-6	2.19 (0.18)	7.09 (0.46)	4.90	0.00
IL-10	11.75 (0.97)	6.88 (0.62)	4.87	0.00
TNF-a	2.00 (0.15)	10.23 (0.43)	8.23	0.00
IFN-g	10.16 (0.44)	10.33 (0.88)	0.16	0.76



## Conclusion

- ❑ The immune abnormalities seen in GWI include immune activation, poor cytotoxic cell function, cytokine regulatory disruptions and abnormalities of neuropeptide Y and cytokines that interface with autonomic, endocrine, and neurologic mediators.
- ❑ Many of the mediators seen are strong enough to be considered as biomarkers for GWI
- ❑ Further, immune activation, pro inflammatory cytokines and factors that promote this steady state of activation and inflammation are reasonable targets for intervention.

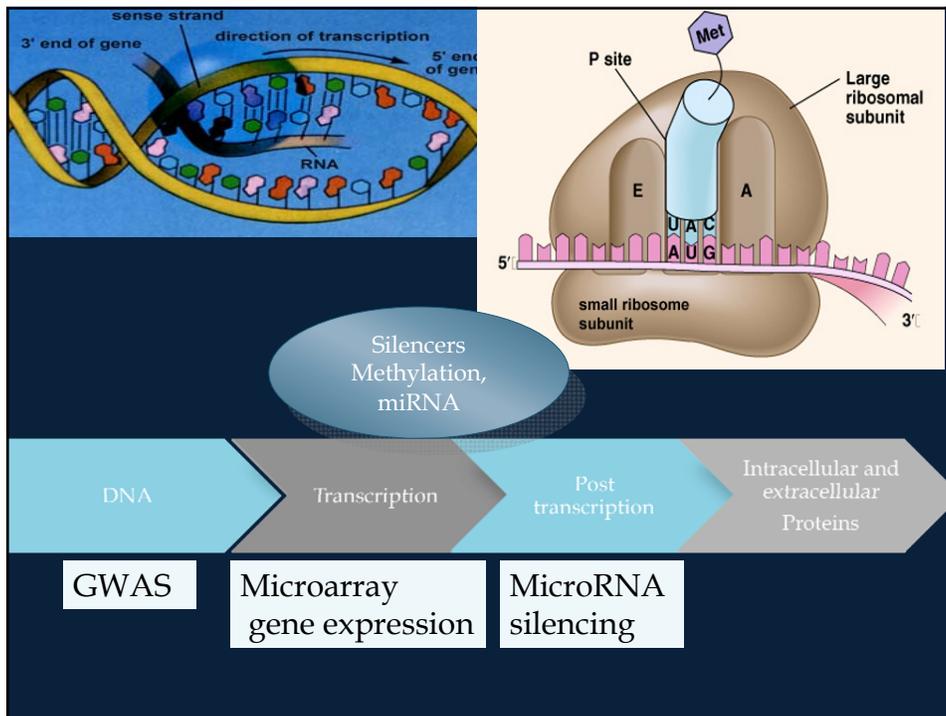
# Gene Environment Interactions

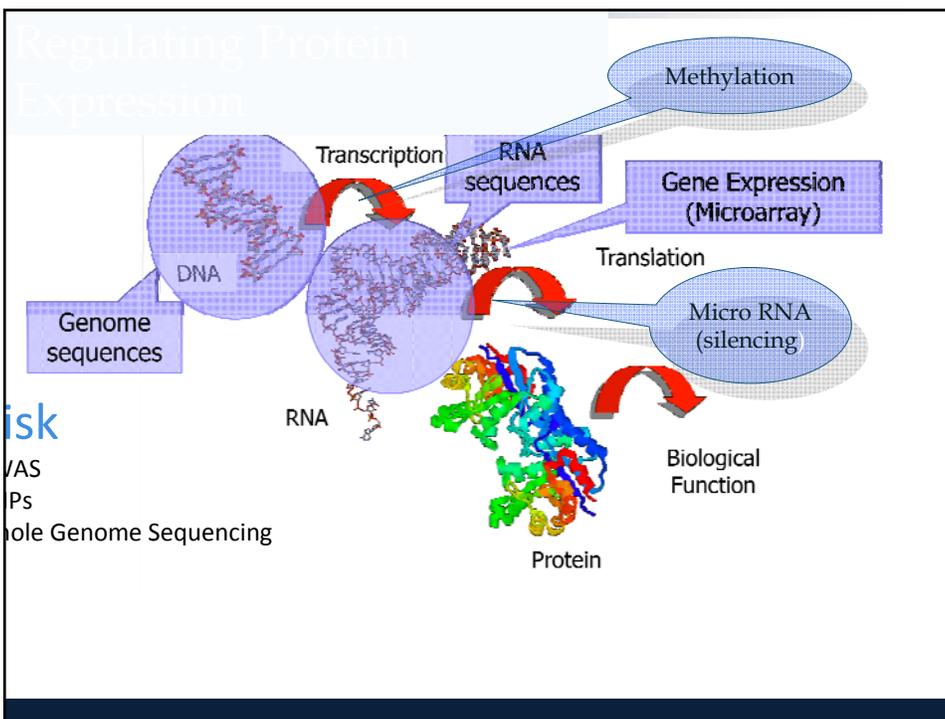


Downs Syndrome

Diabetes  
CFS  
GWI

Fracture  
bone





## Future directions

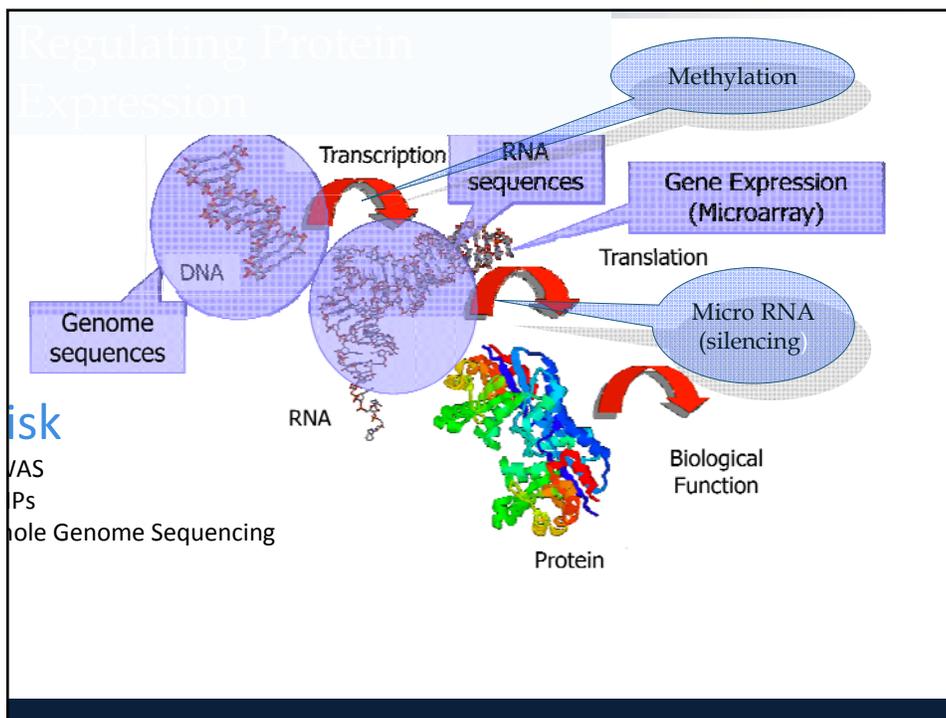
### Complete the data set needed for the comprehensive systems biology analysis of GWI

Underway: DOD study with 8 assessment points post exercise to better map out the systems interactions

Pending review (Merit): Methylation/microRNA analysis of the same cohorts

LOI accepted (DOD): Proteomic/metabolomics study

CSP 585 assessing genetic risk

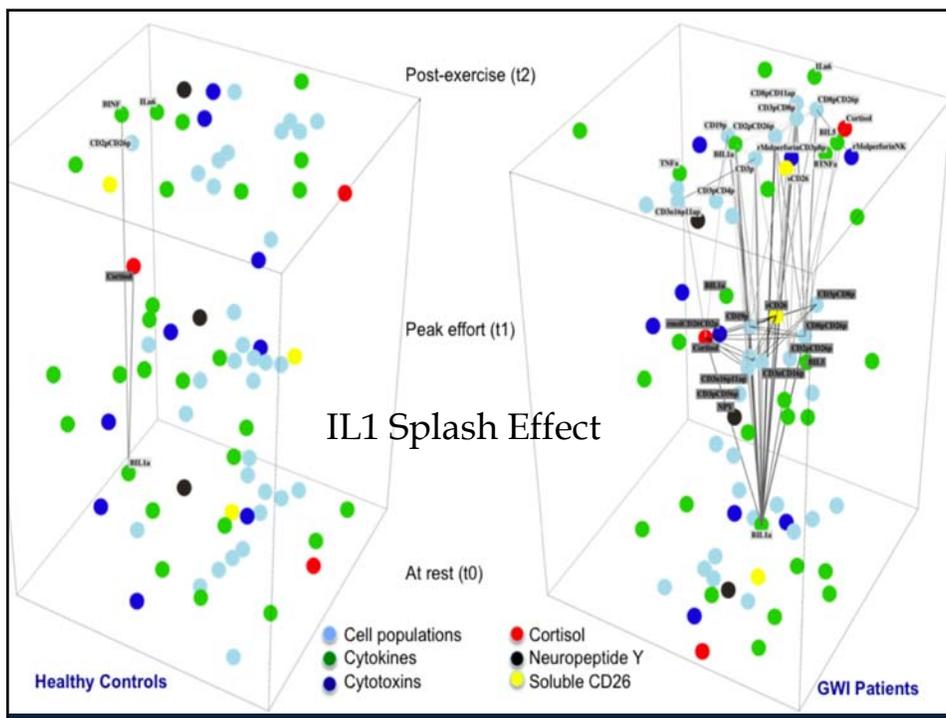


## Future directions

Apply computational models to develop intervention strategies to GWI

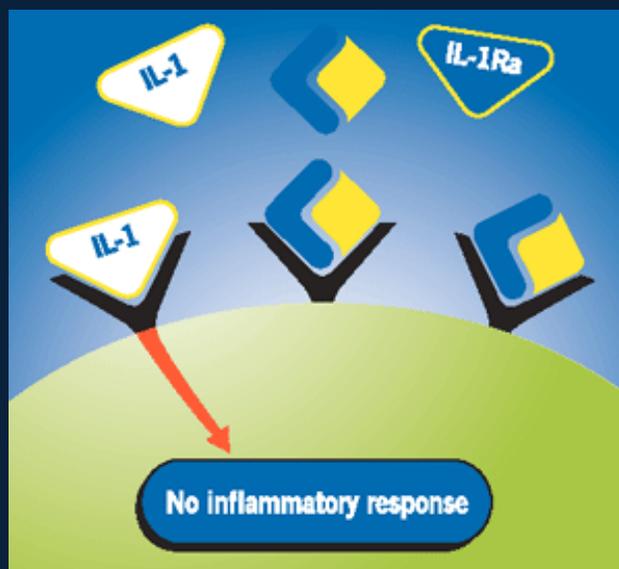
In development: DOD Consortium protocol focused on systems biology/computational modeling in animal and human systems to develop additional models

LOI accepted: Phase 1 trial of IL1 receptor antagonist in GWI

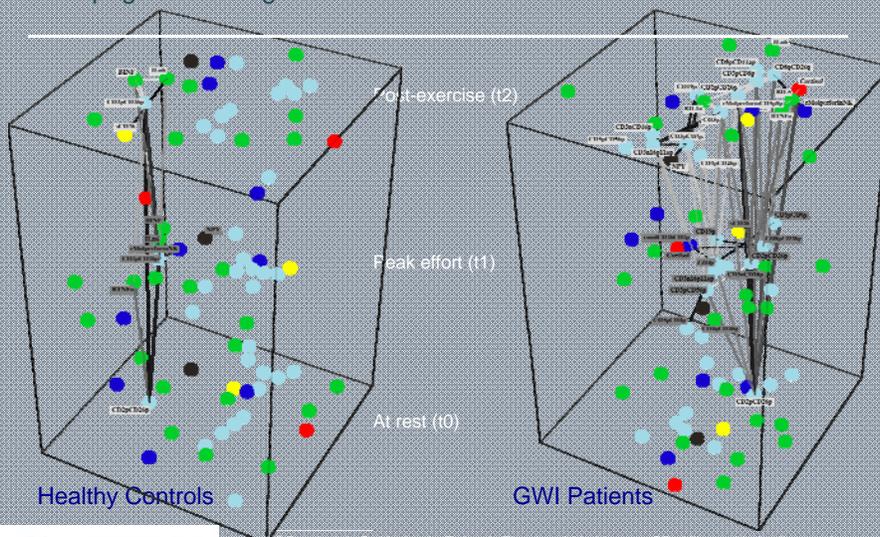


# IL1 receptor antagonist

□

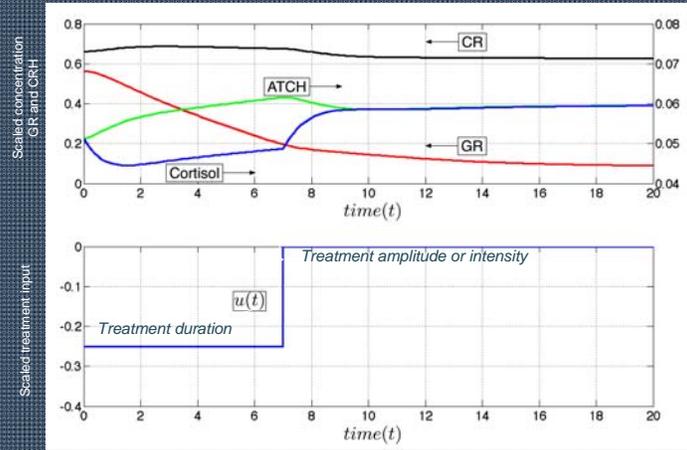


## Propagation through Time of CD2+/CD26+



Broderick G, Kreitz A, Fuite J, Fletcher MA, Vernon SD, Klimas N. A pilot study of immune network remodeling under challenge in Gulf War Illness. *Brain Behav Immun.* 2011 Feb;25(2):302-13.

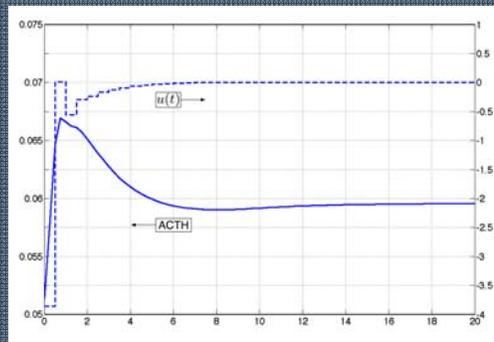
## Sub-optimal Approximation of $u(t)$



Cortisol "sink"

More realistic or practical implementation of numerically optimal treatment

## Optimal Manipulation of HPA Axis



How low and how long:

- Could administer treatment in stages: **looking for a 20% increase in ACTH at rest**
- Smaller reductions in cortisol would require longer treatment
- There is a minimal perturbation however below which the system will simply return to its fatigued state

Time for questions, but first thank you!

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