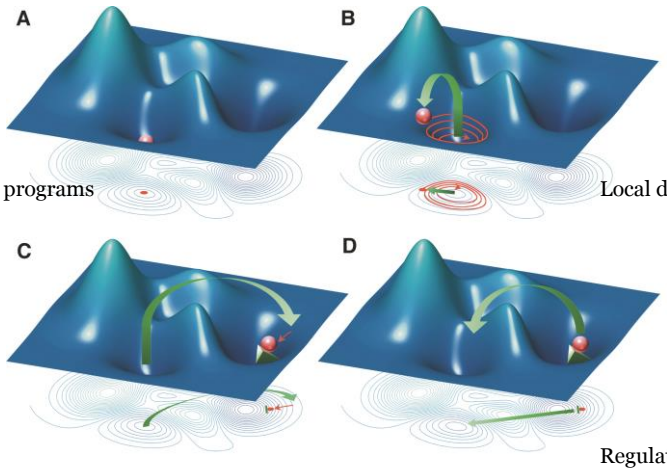
Identifying therapeutic strategies in Gulf War Illness using systems biology

Gordon Broderick, Ph.D., Professor
Travis Craddock, Ph.D., Assistant Professor
Nancy Klimas, MD, Director and Chair Clinical Immunology
Mary Ann Fletcher, PhD, Schemel Professor of Clinical Immunology
Institute for Neuro-immune Medicine, Nova Southeastern University

Persistence and homeostasis



Multiple programs

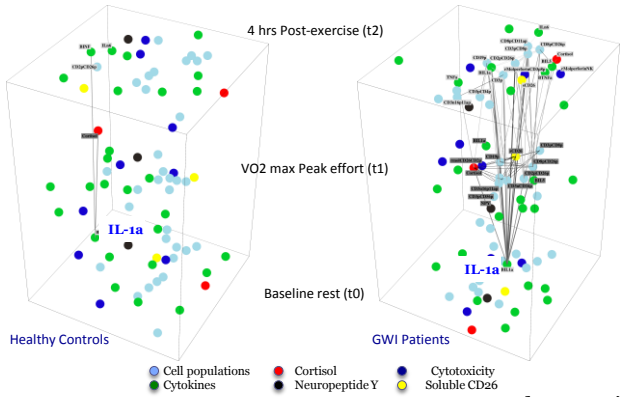
Local dynamics

Insult

Regulatory trap

The mediators

- Characteristic networks *emerge* from small changes



Characteristic IL-1a cascade
(Anakinra *under review by DoD*)

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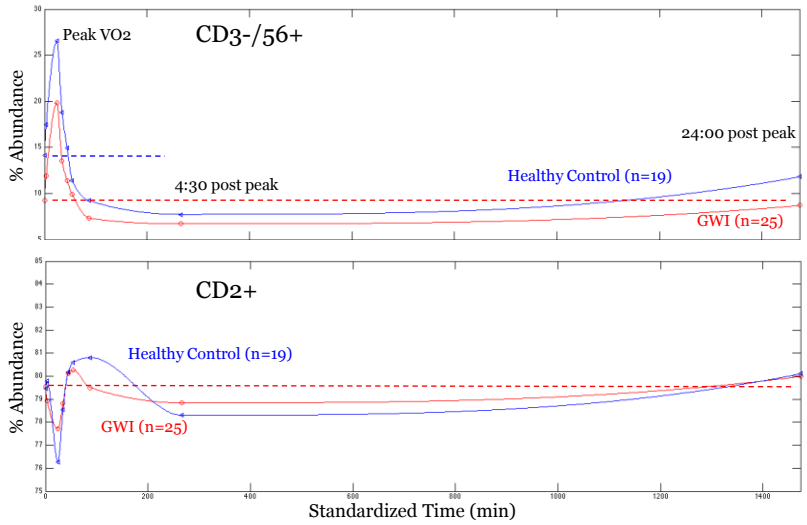
The populations



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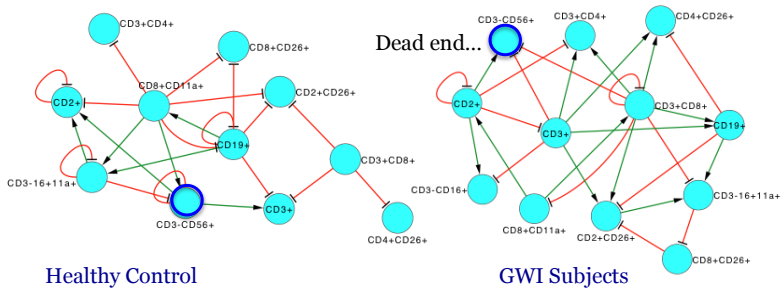
The populations

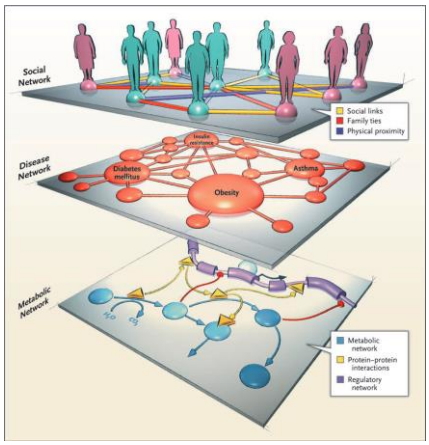
- Evolving structure implies *information flow*



Healthy Control GWI Subjects

Decreased CD3-/56+ NK *information throughput* (betweeness) in GWI

From transcript to behavior

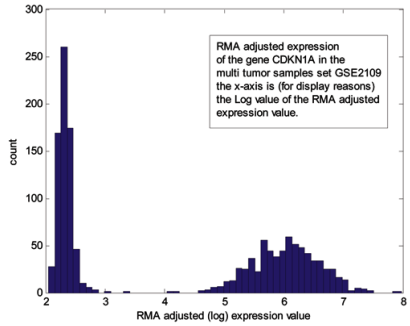


Vertical as well as horizontal integration

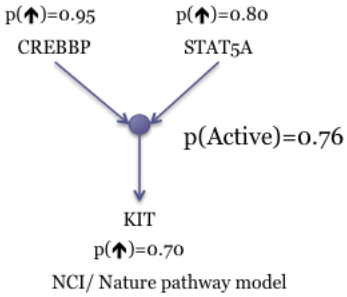
Barabási A.-L. Network Medicine — From Obesity to the "Diseasome". N Engl J Med 2007; 357:4

A transcript-based logic

- Estimating compliance and activity of known pathways



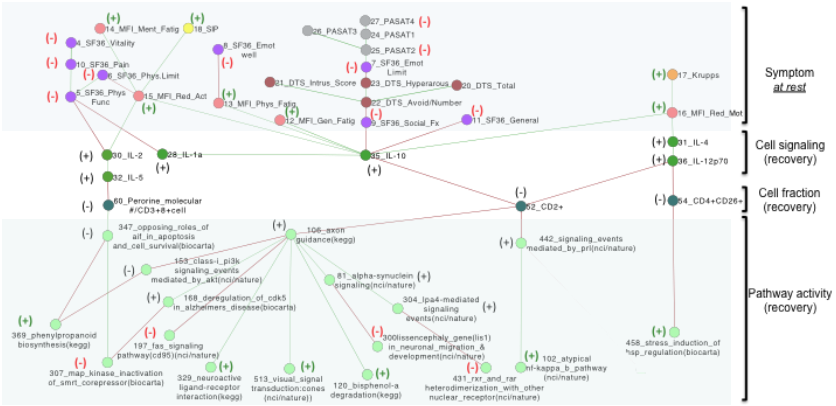
Up and Down states



A discrete pathway logic

From pathway to behavior

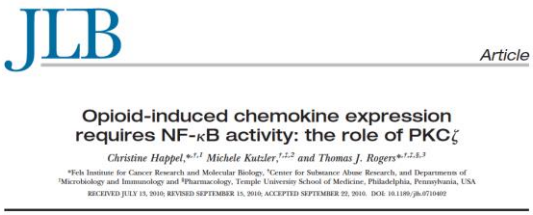
- Quality of life mediated at behavioral interface…



IL-1, IL-10 link fatigue, cognition to neurogenesis and NF-kB activity

Naltrexone and NF-kB

- Mu-opioid receptor (MOR) $\xrightarrow{\text{PLCβ/PKC/IKK}}$ NF-kB induction
- increased IL-1; exaggerated IL-6, TNF-a response to mitogen.


JLB Article

Opioid-induced chemokine expression requires NF-κB activity: the role of PKCζ

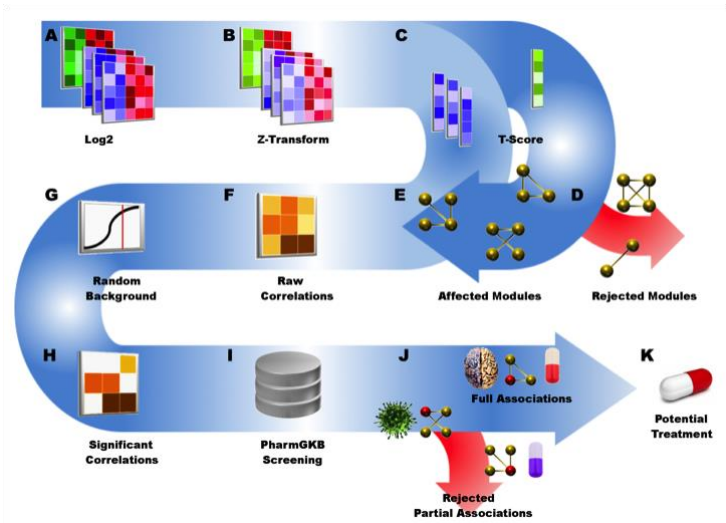
Christine Happel,*,†,1 Michele Kutzler,†,‡,2 and Thomas J. Rogers*,†,‡,§,3

*Felt Institute for Cancer Research and Molecular Biology, †Center for Substance Abuse Research, and Departments of ‡Microbiology and Immunology and §Pharmacology, Temple University School of Medicine, Philadelphia, Pennsylvania, USA

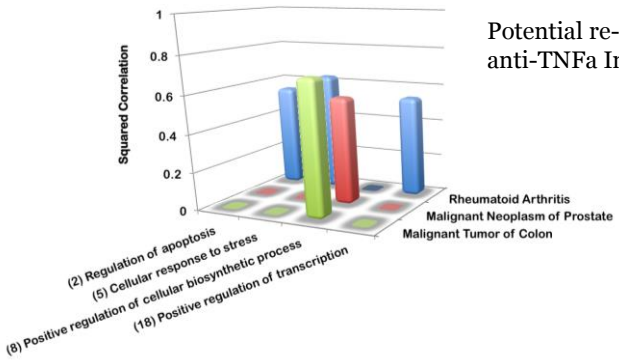
RECEIVED JULY 15, 2010; REVISED SEPTEMBER 15, 2010; ACCEPTED SEPTEMBER 22, 2010. DOI: 10.1189/jlb.0710402

Happel et al., 2011

Mining Drug-action data



Mining Drug-action data



Potential re-purposing of anti-TNFa Infliximab

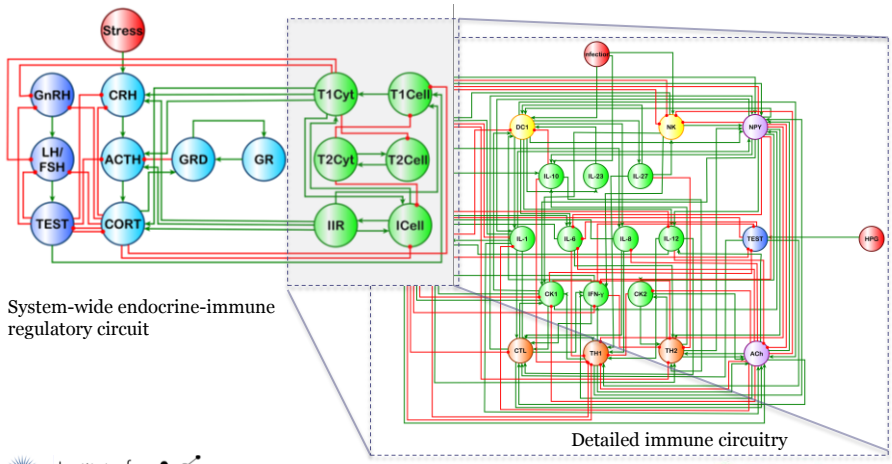
Significant correlation r^2 of Gulf War Illness with 3 of 54 candidate illnesses based on gene expression in 4 of 54 DAVID functional modules GEO database

Emerging avenues

- Candidate targets
  - IL-1 modulation of inflammatory cascade (Anakinra –*under review by DoD*)
  - NF-kB modulation (μ-opioid receptor antagonist Naltrexone)
  - Re-purposing from RA of anti-TNFa (Infliximab)
- But *how* exactly should these be manipulated?

Using what we know

- *directed* interaction meets *a priori* knowledge



System-wide endocrine-immune regulatory circuit

Detailed immune circuitry

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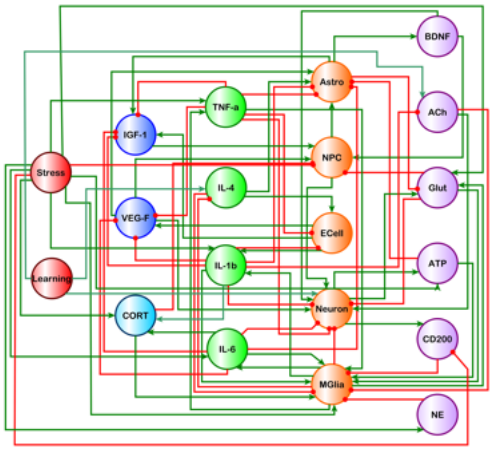
Using what we know

- Simulating neuro-inflammation using *a priori* knowledge



A first prototype circuit model describing the regulation of neuro-inflammation

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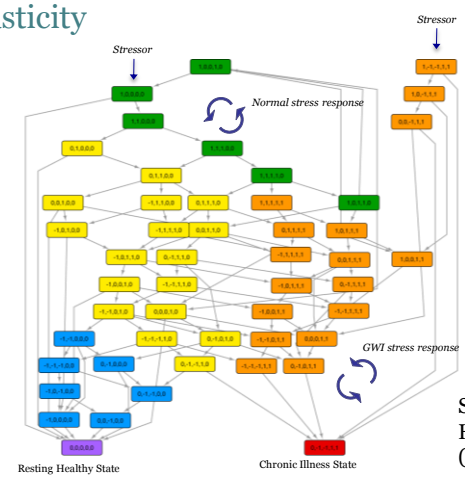
Regulatory contribution

- Regulatory contribution: overlap with naturally occurring regimes
  - Depressed testosterone
  - Elevated cortisol, NPY
  - Pro-inflammatory immune signature (classic Th1 and Th17)
  - Align with persistent neuro-inflammatory cascade
- Compounded by altered wiring – epigenetic modifications?

Frame by frame sequence

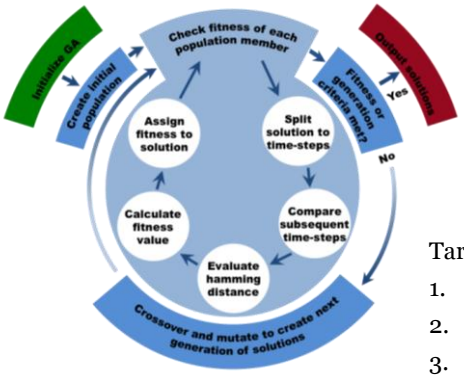
- Alternate realities of neuroendocrine-immune plasticity



Stability analysis of HPA-HPG-immune co-regulation (Craddock et al., 2014)

Treatment trajectory

Solution gene = k •T bits



Target combines *multiple objectives*:

1. Solution must adhere to model
2. Converge to healthy stable point
3. Be minimally invasive

Emerging avenues

- Designing interventions that make optimal use of the body's own "regulatory pull"
  - Early simulations indicate coordinated manipulation of multiple targets may be required.
  - Targets include combined GR blockade and Th1 modulation (e.g. anti-TNFa)
  - So far no viable single-point intervention escapes regulatory pull

Using a little muscle

Supercomputer to bedside

One week run time on 7000 CPU generating 0.3 TB of data

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Building momentum with critical mass

GWIRP WSU Sarin mouse model

CDC Cortisol/DFP mouse model

GWIRP "Fight or Flight" Dysfunction

GWIRP Network Dynamics under Challenge

***Study 1 (mouse)**: Mechanisms of autonomic neural/adrenal dysfunction*

***Study 2 (mouse):** Molecular phenotype - stress, exposure and brain immunity*

***Study 3 (computer):** Integrating human and animal research through systems biology*

***Study 4 (animals):** Link to drug libraries to evaluate suggested therapeutics.*

***Study 5 (veterans):** Translational human clinical trials to achieve* regulatory "reset" and recover exercise response

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