Identifying therapeutic strategies in Gulf War Illness using systems biology

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Persistence and homeostasis

A
Multiple programs

B
Local dynamics

C
Insult

D
Regulatory trap
The mediators

- Characteristic networks *emerge* from small changes

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

The populations

[Graphs showing % Abundance of CD3-/56+ and CD2+ cell populations with time in minutes.]

Healthy Control (n=19)
GWI (n=25)
The populations

- Evolving structure implies *information flow*

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Healthy Control

GWI Subjects

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

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From transcript to behavior

Vertical as well as horizontal integration

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A transcript-based logic

- Estimating compliance and activity of known pathways

### Figure

- **CREBBP**
  - $p(\uparrow) = 0.95$
- **STAT5A**
  - $p(\uparrow) = 0.80$
- **KIT**
  - $p(\uparrow) = 0.70$
- **Active**
  - $p(\text{Active}) = 0.76$

**NCI/Nature pathway model**

**Up and Down states**

**A discrete pathway logic**

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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-κB

- Mu-opioid receptor (MOR) → NF-κB induction
- increased IL-1β; exaggerated IL-6, TNF-α response to mitogen.

Happel et al., 2011

Mining Drug-action data
Mining Drug-action data

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-TNFα (Infliximab)

- But *how* exactly should these be manipulated?
Using what we know

- **directed interaction** meets *a priori* knowledge

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

\[ k \text{ state variables} \]

\[ t = 1 \quad \ldots \quad t = 2 \quad t = T \]

Solution gene = \( k \times T \) 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-TNFα)
  - So far no viable single-point intervention escapes regulatory pull
Using a little muscle

Pegasus Platform
CCS University of Miami

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

Building momentum with critical mass

GWIRP WSU Sarin mouse model
GWIRP “Fight or Flight” Dysfunction

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

GWIRP Network Dynamics under Challenge

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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