From Modeling to Clinical Trials: The Etanercept/Mifepristone Studies

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NSU Institute for Neuro Immune Medicine: Moving Knowledge to Treatment

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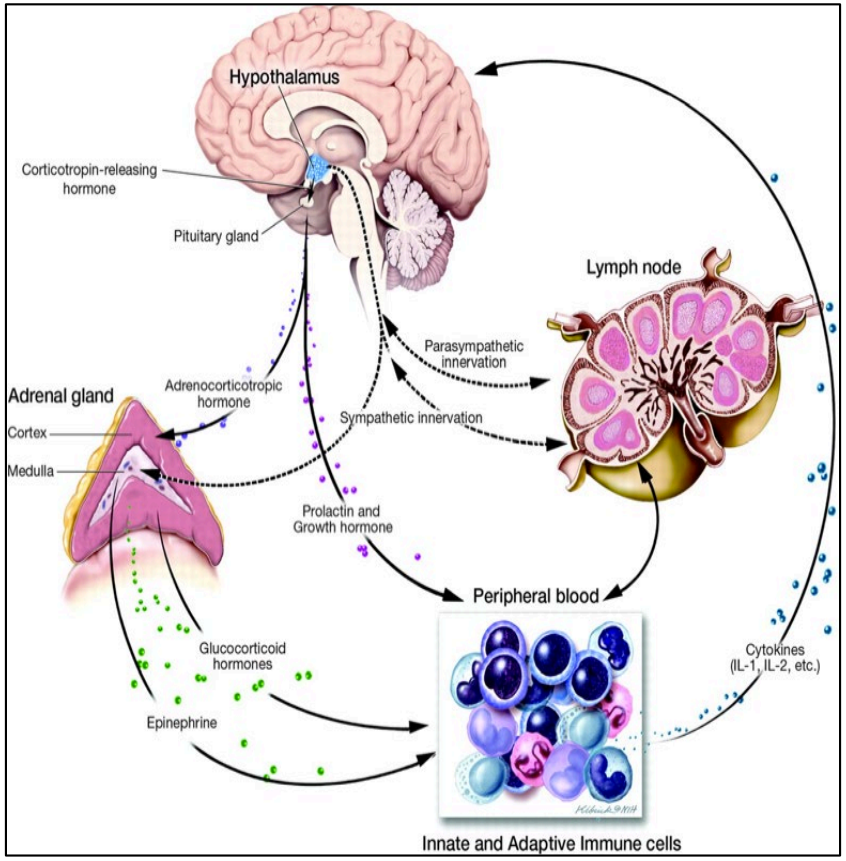
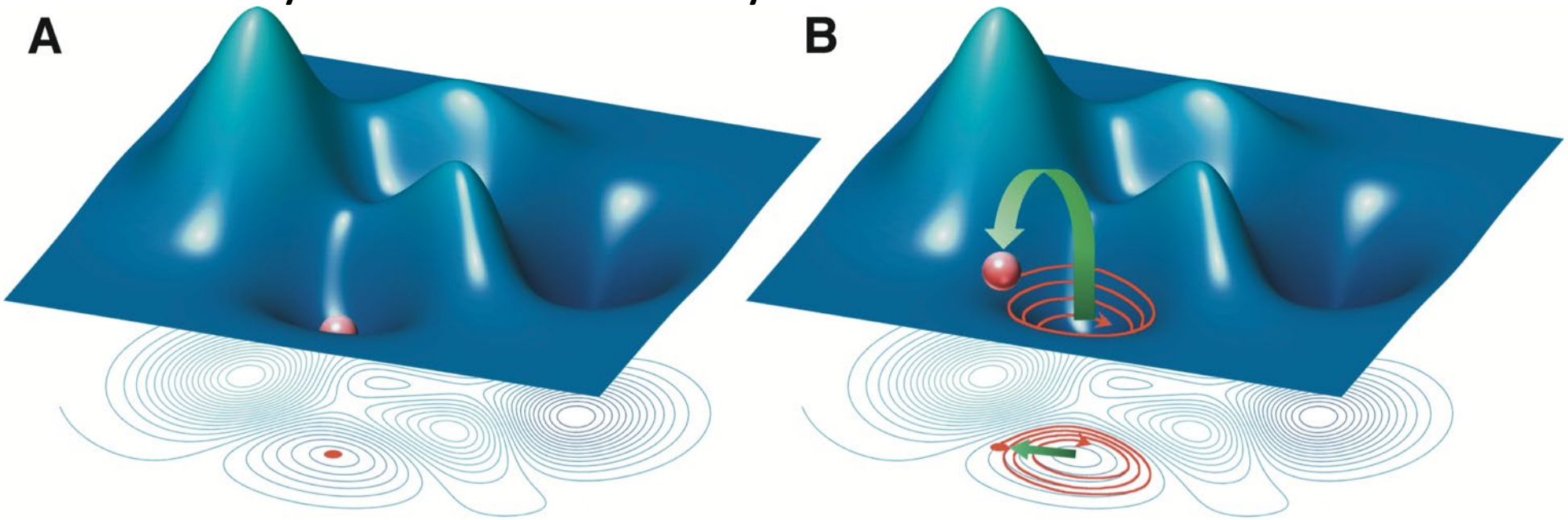
Going for the cure:
Optimizing treatment course to reset system homeostasis

- Key systems:
  - Immune system
  - Endocrine System
  - Nervous System
- All 3 systems intercommunicate.
- All systems must be considered.
- Multisymptom illness indicates multiple system involvement.
- **<u>One</u>** intervention may not be enough



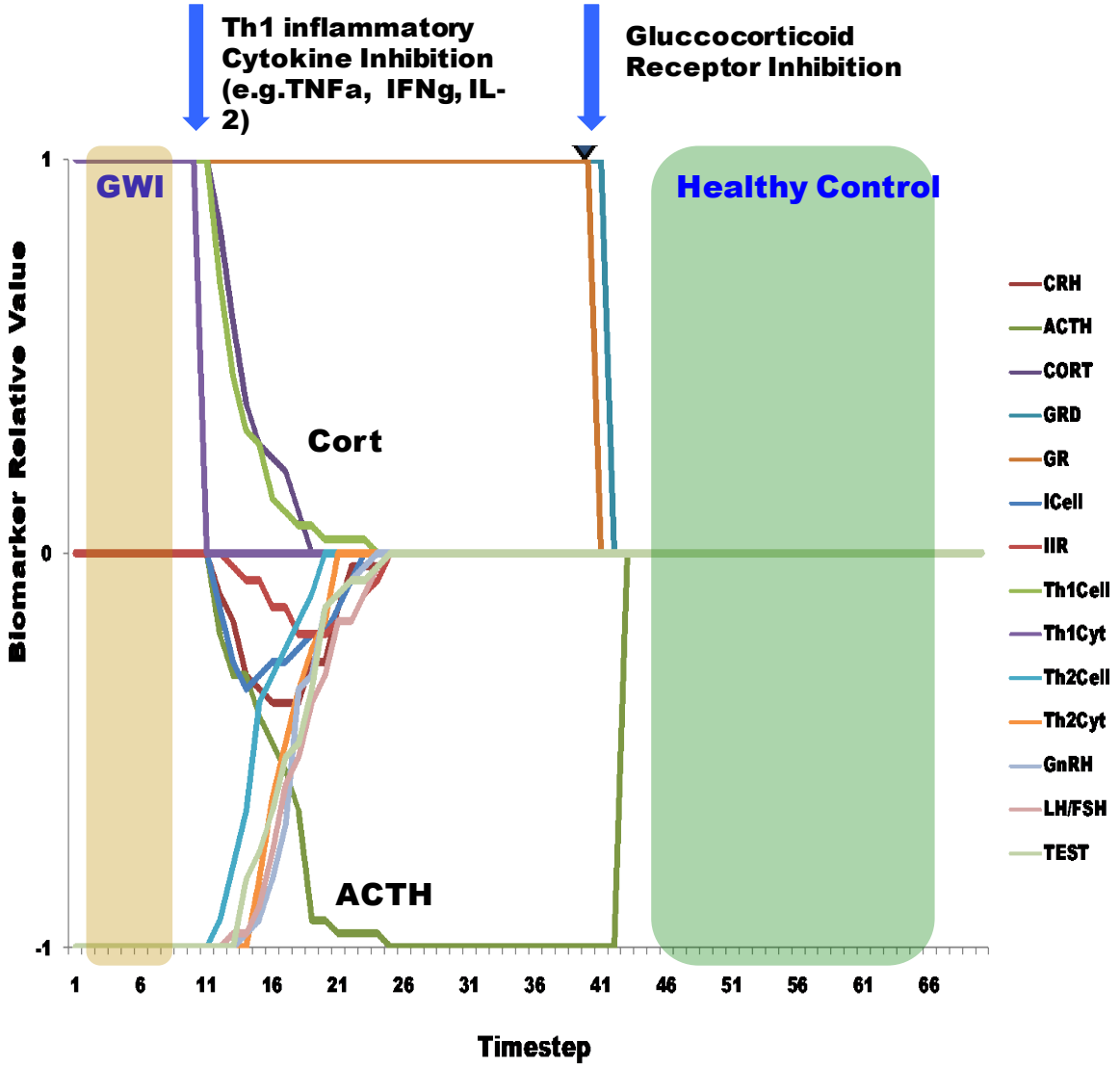
Hypothesis: Complex System – Multiple Homeostatic states

- Complexity gives rise to multiple stable behaviors
- Typical external factors perturb the system, which eventually returns to stability



Fritsch et al.(2013). Exploring the sometimes pathogenic versatility of discrete immune logic. *Systems Biomedicine*, *1*(3), 179-194.

TREATABLE: DELIVERING LASTING REMISSION



Integrating basic science with clinical data… *one-two endocrine-immune punch*

Etanercept/Mifepristone Phase I/II Study Research Strategy: Objectives

- The Phase I/II studies proposed build upon our earlier research efforts evaluating this drug combination in this population.

- Specifically, in these Phase I/II studies, we aim to find the most effective dosing and duration regimen for etanercept and mifepristone combination therapy, and to move it immediately into a Phase II placebo-controlled evaluation.

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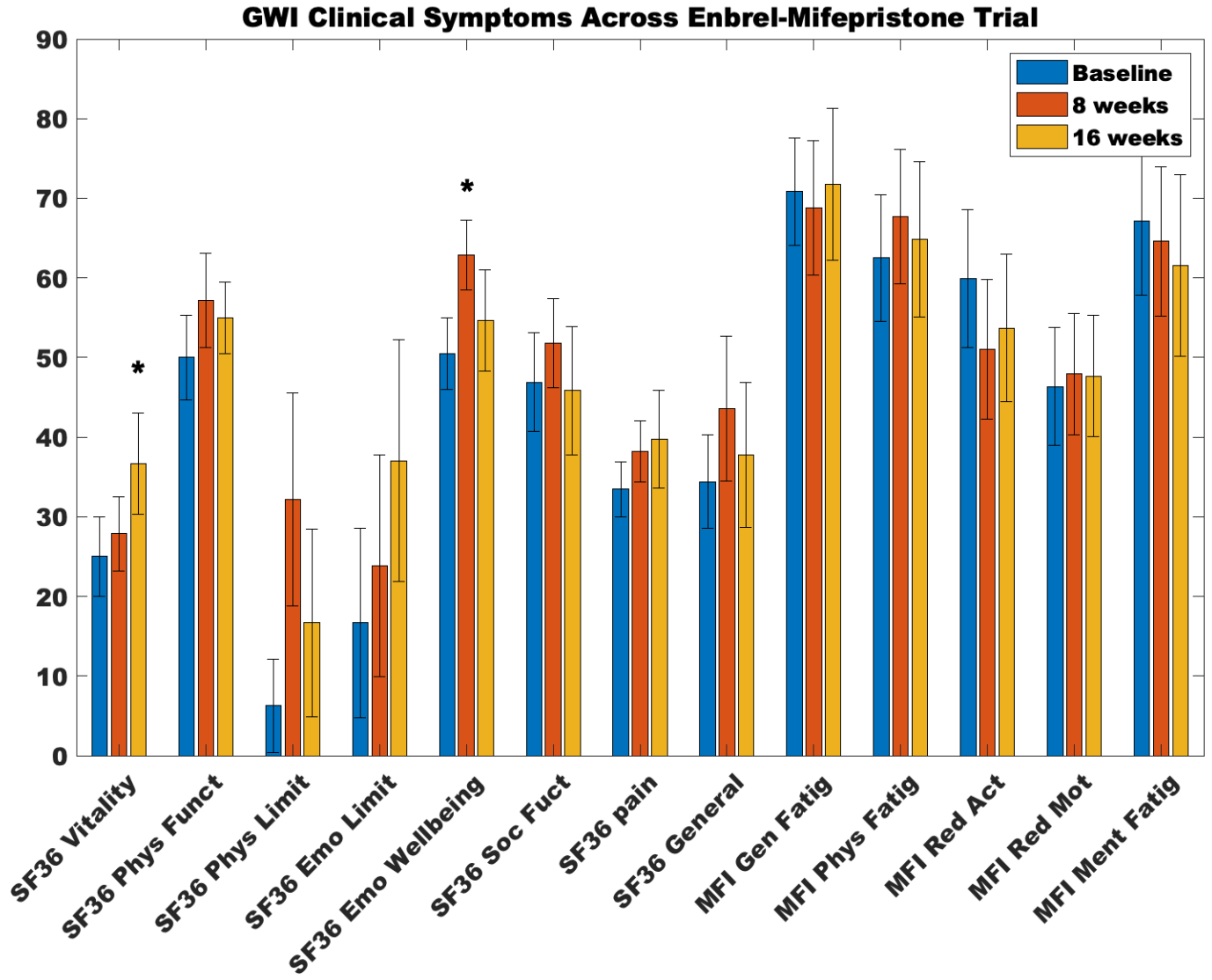
Clinical Symptoms

- Preliminary results from 9 males GWI subjects undergoing Enbrel-Mifepristone
- Assessments made at: baseline, immediately after Enbrel-Mifepristone (8 weeks), and follow-up (16 weeks)
- Vitality improved out to 16 weeks.
- Emotional wellbeing improved immediately after protocol end



* $p < 0.05$ compared to baseline

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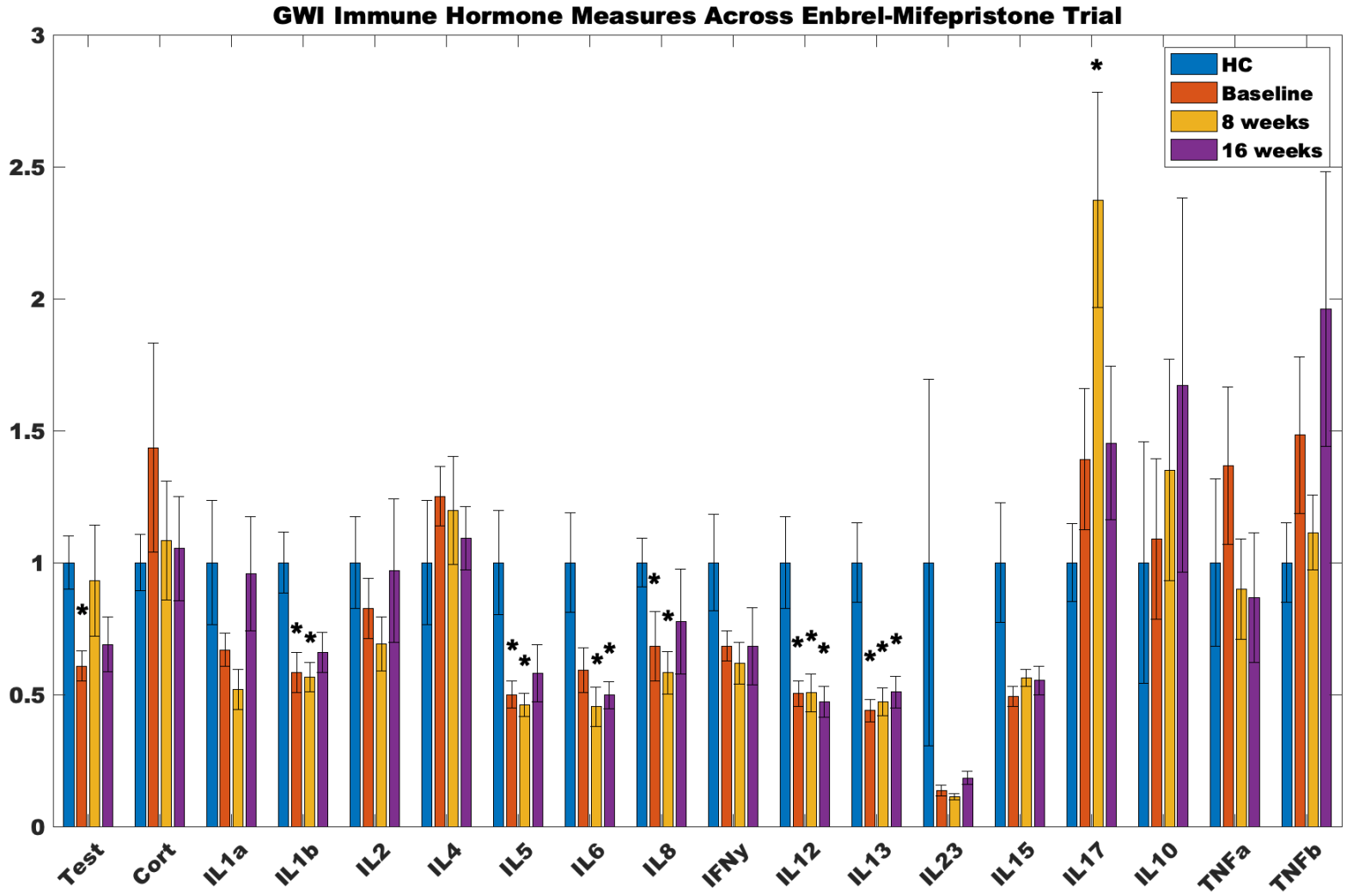
Hormone & Immune

- Preliminary results from 9 males GWI subjects undergoing Enbrel-Mifepristone
- 9 age and BMI matched healthy controls (HC) from DoD GWI male study for comparison
- Assessments made at: baseline, immediately after Enbrel-Mifepristone (8 weeks), and follow-up (16 weeks)
- Hormones moved closer to control across study
- Trends for IL1a, IL2, IL4, IL8, and TNF moved closer to HC
- IL10, TNFb moved away from HC
- Remainder appear to be unaltered



* $p < 0.05$ compared to HC
All values normalized to HC

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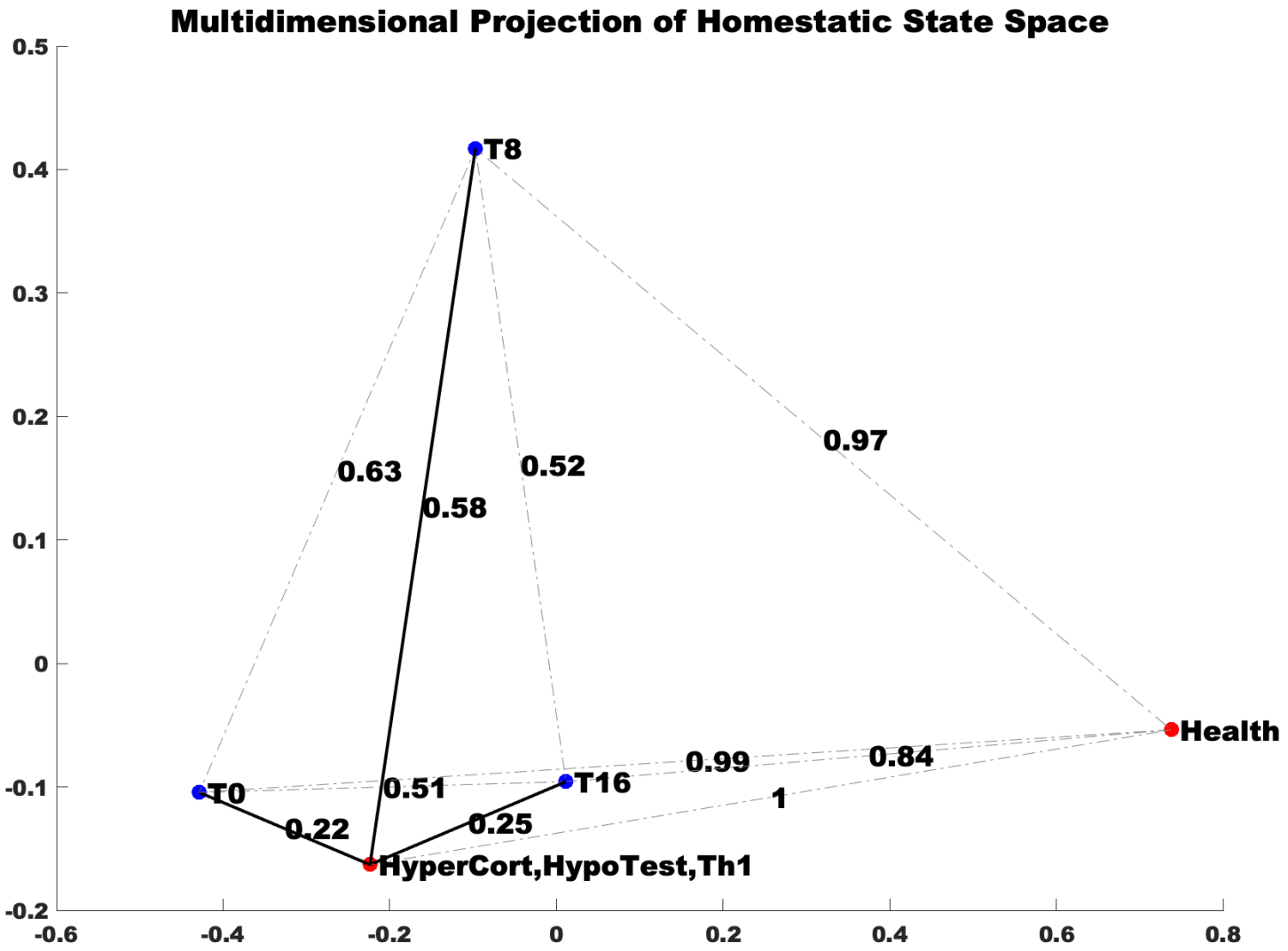
Homeostatic Reset

- Preliminary results from 9 males GWI subjects undergoing Enbrel-Mifepristone
- Hormone-Immune profiles of GWI over trial compared to controls based on healthy and hypercortisolic, hypoadrenergic and Th1 state
- All timepoints of trial remain in orbit of hypercortisolic, hypoadrenergic and Th1 state
- However, proximity of timepoints move closer to health across study
- Indicates improvement, but not homeostatic reset



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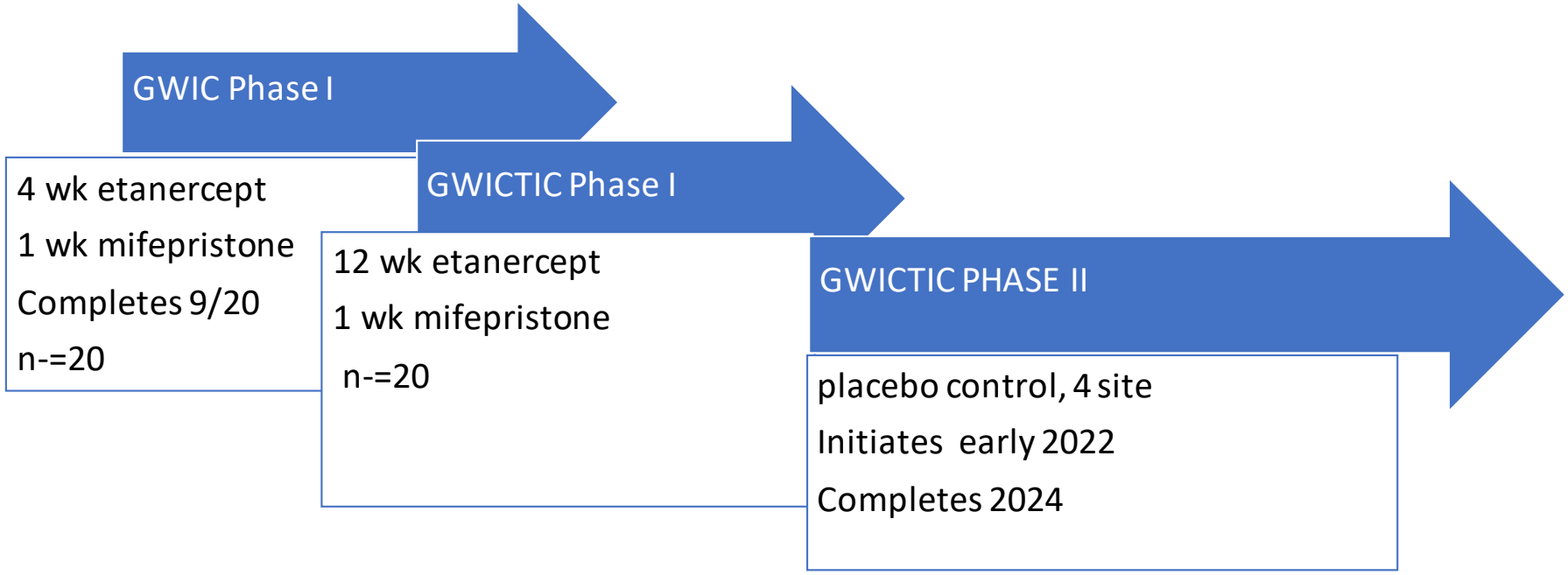
Best of two models moving forward to phase 2

- These initial findings are promising, with clinical, biologic and homeostatic improvement, though in an N of 9.(GWIC)
- This initial study will be complete in June of 2021 (N=18)
- A second phase 1 study is initiating with a longer duration of etanercept (3 mo) and a higher dose of mifepristone (GWICTIC)
- The most effective of these two strategies will move forward to phase 2 in FY 2022 through the CDMRP funded GWICTIC.

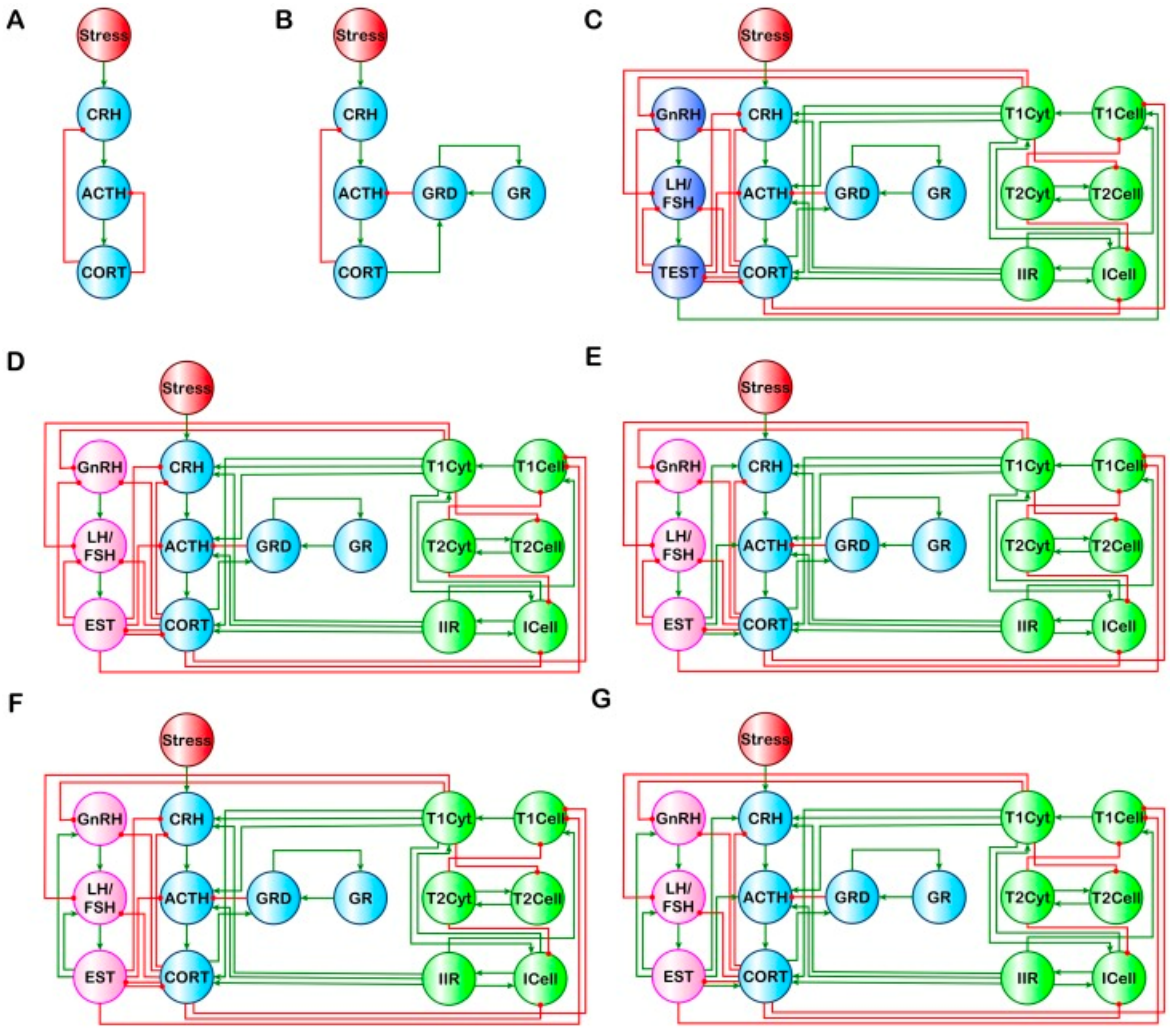
Etanercept/Mifepristone Phase I/II: Phase I and II studies of the “reboot” strategy

In order to reduce the administrative time anticipated in a Phase I to Phase II design, we compressed the 2 protocols, and submitted them to the IRP, the IRB and HRPO (initially for prereview, then for final review).

The design requires a Phase I phase of etanercept/mifepristone that will be compared to a shorter duration of treatment Phase I study currently underway. The results are analyzed and the more effective strategy moves forward to the Phase II placebo controls study. This final design will be re-reviewed by the external review panel, IRB, and HRPO, but we anticipate a quick process, as a simple amendment.



Gender differences will the eventual treatments be different in men and women?

- 

Standard and extended HPA models.
(A) Standard HPA model.(
(B) B) HPA-GR model of Gupta et al.
(C)
Integrated models
(C) HPA-GR-Immune-HPGa for males,
and
(D) HPA-GR-Immune-HPGb,
(E) HPA-GR-Immune-HPGc,
(F) HPA-GR-Immune-HPGd, and
(G) HPA-GR-Immune-HPGe for females.

For (C) – (G) connections between the sex steroid EST and the HPG and HPA components change between stimulatory and inhibitory to capture the effects of the menstrual cycle.

Discussion points

- We have committed to repurposed drugs on formulary in our efforts to expedite delivery therapies to GWI veterans 30 years into their illness.
- Etanercept is on formulary, and the generic was approved by the FDA last year.
- Mifepristone is a unique drug, a glucocorticoid receptor antagonist used to treat Cushings disorder. This is a highly restricted drug but available on formulary.
- The GWICTIC structure allows for rapid movement through phase 1 and 2 studies. If the phase 1 study is promising it is already funded, and an expedited review by the EAB will allow progression to the phase 2 study as early as next January.
- We provide an annual research updates conference for all of the study participants in this and past studies to inform them of progress, we frequently have 800 or more registrants in these conferences. We also have a larger registry of 3,500 veterans interested in participating in research studies who receive quarterly newsletters and engage in our social media outreach (Facebook, twitter, etc)
- We have discussed this with the FDA, requested an IND exception, granted. Because there are phase 3 funding mechanisms in the VA and the CDMRP we do not require full funding with a pharmaceutical partner to complete all steps through to approval.