Targeted therapeutics in GWI: Status report on CoQ10 and Rituximab Trials

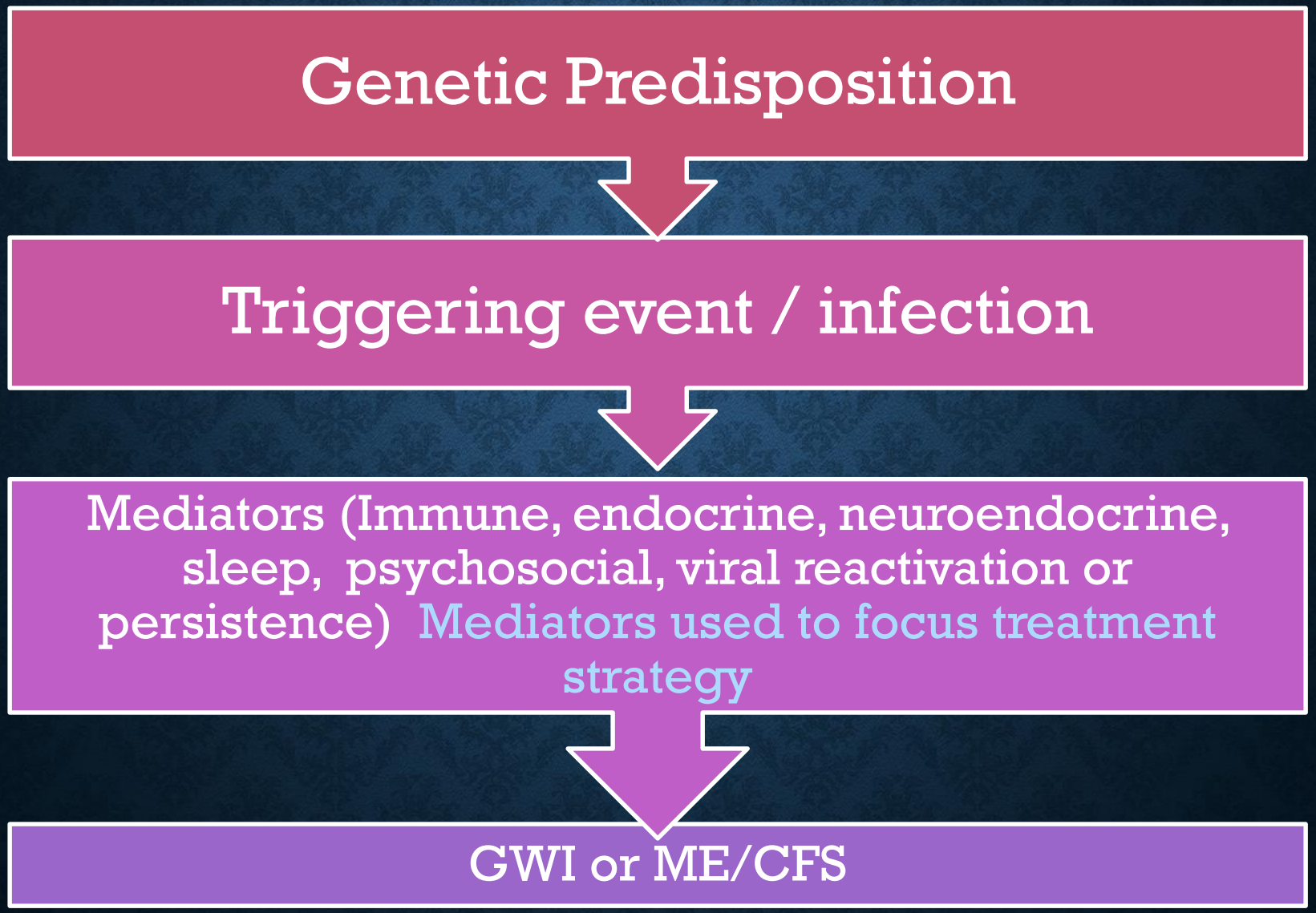
Nancy Klimas, MD
Nova Southeastern University
Miami VA Medical Center
Institute for Neuro-Immune Medicine
(NSU INIM)
Representing
The NSU Institute for Neuro-Immune Medicine
Mary Ann Fletcher, PhD, Lubov Nathanson, PhD, Gordon Broderick, PhD, Travis Craddock, PhD and the INIM team

About one-third of Gulf War veterans — or 175,000 to 250,000 have Gulf War illness. USA TODAY

TWO ILLNESSES WITH SIMILAR CLINICAL PRESENTATION

Gulf War Illness **300,000 US veterans**	**Chronic Fatigue Syndrome** **1,000,000+ US citizens**
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 Weight loss, low grade fever	Tender lymph nodes Systemic Exertion Intolerance Disease SEID 1 and 2 plus cognitive or autonomic findings

MODEL OF PATHOGENESIS



Immune abnormalities common to both GWI and CFS/ME

Immune Activation

- DR, CD26, CD 38 expression
- TH2 cytokine shift
- Pro-inflammatory cytokines expression TNF-a, IL-1, IL6
- NPY elevation,
- Neuro inflammation by imaging

Functional defects

NK Cell dysfunction

CD8 abnormalities

↓Perforins, Granzymes

Macrophage abnormalities

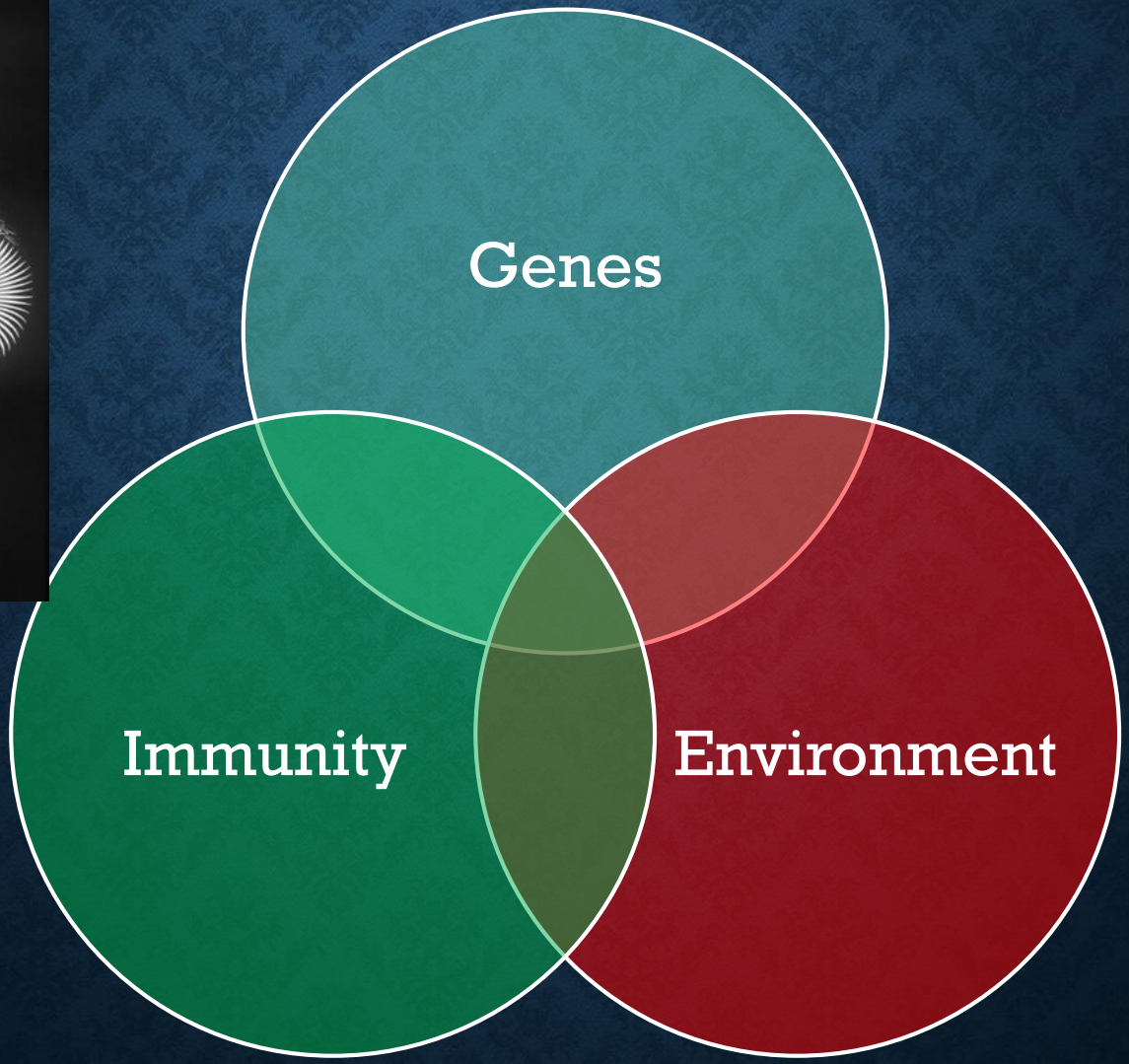
Antibody production

Mitochondrial dysfunction

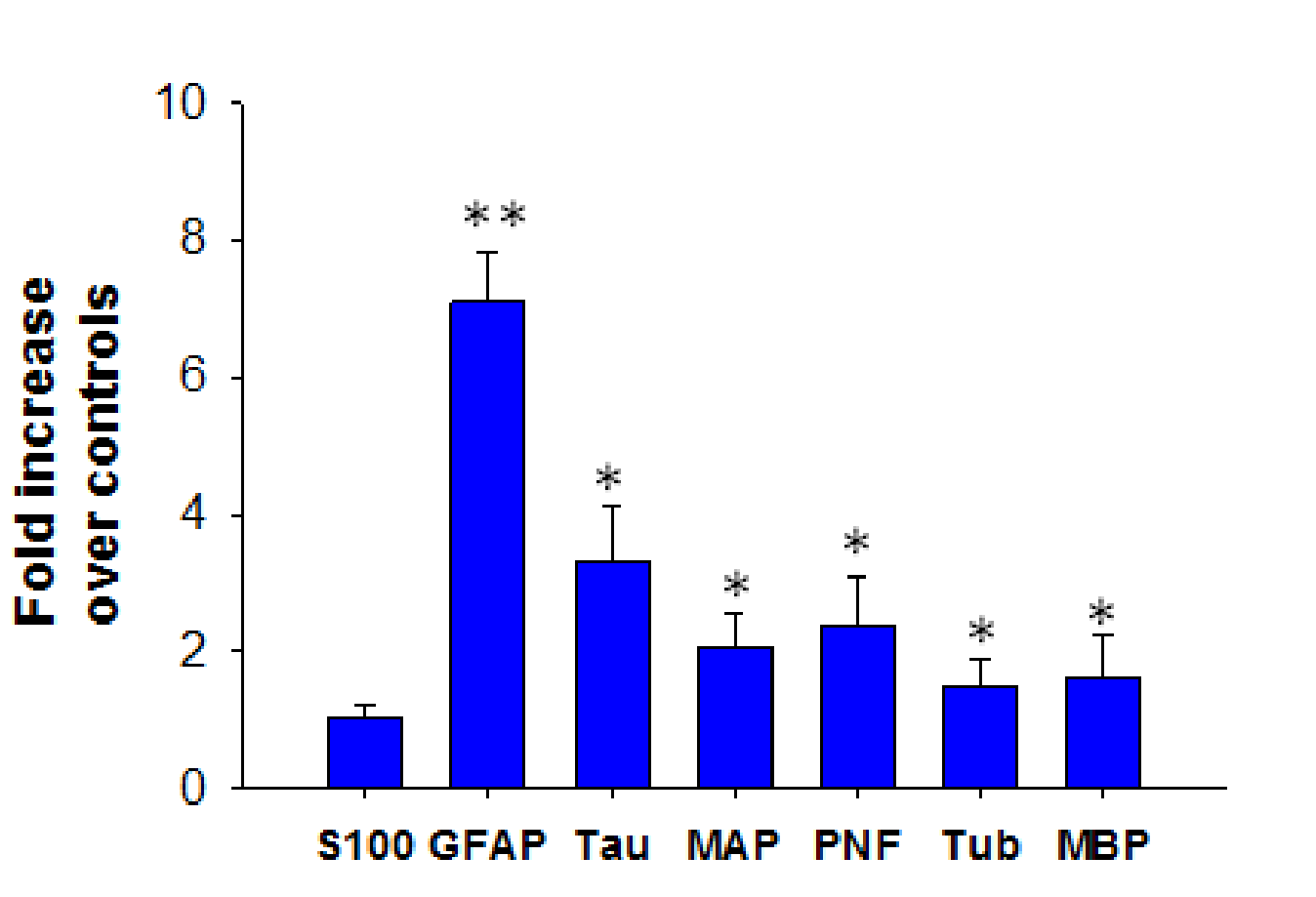
THE USE OF B CELL DEPLETION IN THE TREATMENT OF GWI

- Promising phase 2 study on ME/CFS
- Similar immune signature, suggesting autoimmune process
- Auto antibody studies of Dr Abou Donia and Kim Sullivan suggests CNS autoantibodies could play an important role in a large subset of GWI
- Earlier studies of anti-GAD antibody also suggest this model

AUTOIMMUNITY



THE ROLE OF AUTOANTIBODIES IN GWI



Fold differences

CaMKII 9.27,
GFAP 6.60,
Tau 4.83,
Tubulin 4.41,
MAG 3.60,
MBP 2.50,
NFP 2.45,
MAP-2 2.30,
S-100B 1.03

Abou Donia et al 2017

RITUXIMAB IN ME/CFS

- Two phase 2 studies (Fluge and Mella)
- Phase 3 study using repeated dosing underway
- In those that improved, there was a marked improvement in function, highly durable (25 Months to 44 Months) , 64% of 29 in open label phase 2, 67% of 15 in placebo control trial (13% placebo benefit)

- No autoantibody clearly predictive

OBJECTIVES

- 1. To evaluate the safety of rituximab, relative to placebo in GWI
- 2. To evaluate the effect of rituximab, relative to placebo, on changes in Short Form-36 (SF-36) combined physical health summary and vitality subscale scores relative to baseline during nine month follow up
- 3. To determine the predictive value of CNS autoantibodies levels against neuronal glial proteins in responders and nonresponders.

DESIGN

- Double blind placebo control
- **40 veterans with GWI, 20 in each group,** matched for age +/- 5y, body mass index +/-5 (BMI), ethnicity and gender
- This study will compare treatment with rituximab or saline solution; two infusions with two weeks' interval (500 mg/m2, max. 1000 mg), followed by nine months of observation and assessment.
- 9 month observation

OUTCOME VARIABLES

Primary: **SF36 vitality and physical function** sub scores,

Secondary:

Neurocognitive function scores (To, six week, three month, six month, and nine month visit),

Self-reported fatigue score monthly

Physical activity using a Fitbit Charge device that also gives measures of rest (sleep) and pulse,

Fatigue severity scale (FSS)

Clinical response duration defined as consecutive self-recorded fatigue score improvement of at least 4.5 for a minimum of four weeks, as used in the Norwegian CFS/ME studies.

LAB MEASURES (BASELINE, SIX WEEKS, THREE MONTHS, SIX MONTHS, NINE MONTHS)

- Focus on safety and mediators
- **Safety –** CBC, renal and liver function, electrolytes, u/a
- **Cytokines:** The culture supernatants will be harvested for analyses of cytokines (18 cytokine multiplex panel),
- NPY, and epinephrine, norepinephrine.
- **Flow cytometry:** Subsets the panel focuses on activation markers, naïve vs. memory populations, markers of apoptosis.
- **Natural killer cell function,** whole blood assay, same day as draw

LAB MEASURES

- **Gene expression by NanoString:** We will use a NanoString nCounter of 450 genes selected from our previous work with GWI and 15 internal reference genes. .
- **Hypothalamic-pituitary-adrenal (HPA) axis:** Four salivary cortisol levels are assessed at each time point, to evaluate diurnal expression.
- **Hypothalamic-pituitary-gonadal (HPG) axis:** Serum testosterone levels, estrogen, luteinizing hormone and progesterone
- **Hypothalamic-pituitary-thyroid (HPT) axis.** TSH, free T4 and free T3.
- **Autoantibodies Determination** neurofilament proteins, microtubule associated protein-2 (MAP-2), microtubule associated protein tau (TAU), tubulin, myelin basic protein (MBP), glial fibrillary acidic protein (GFAP), and glial S100B protein.

STATUS REPORT : RITUXIMAB STUDY

Study personnel on board, trained

Redcap platform up and tested

Protocol revisions responsive to critique incorporated

FDA IND exclusion obtained

NSU IRB submitted, initial questions answered

Full approval expected mid August

HRPO review at that point

CDMRP budget the finalized for approval

Initiation anticipated October 2017

CO Q 10 OVERVIEW

- Background
- Early Phase I/II Clinical Trial of CoQ10 Results
- Importance of Coenzyme Q10
- Comparison of Phase I/II and Phase III Trials
- New Phase III Clinical Trial Research Design
    - Research Objectives, Aims, and Outcomes
    - Phase III Recruitment, Eligibility, and Exclusion Criteria
- Timeline: Next Steps for Study Implementation
- Future Collaborative Clinical Trials

BACKGROUND

- Gulf War veterans experienced environmental exposures that are known to contribute to cell injury.
- Studies revealed problems with detoxification pathways which suggest interventions that will prevent or repair cell function.
- Studies using exercise challenge show rapid anaerobic state with free radical/oxidative stress pathway activation
- **Early study: Phase I/II Clinical Trial of CoQ10 in Patients with Gulf War Illness (GWI) (Golomb, 2014)**

PHASE I/II COQ10 CLINICAL TRIAL OVERALL RESULTS

- Significant improvement in men with Gulf War Illness as compared to subjects taking placebo (no drug) based on general self-related health (GSRH).
- A rise in CoQ10 levels approached statistical significance as a predictor of improved general health (GSRH) and significantly predicted better physical function in men.
- Women did not experience the same degree of improvement as men (very small N).
- Subjects taking 300 mg experienced activating effects of night-time split dose, interfering with sleep.

PHASE I/II COQ10 STUDY RESULTS SPECIFIC GROUPS

Study Conclusion: CoQ10 provided benefit to physical function and symptoms in veterans with GWI and a study with a larger sample is warranted.

A larger sample is needed to see the effect of interesting findings:

- In the placebo group, higher ratings of general health at baseline predicted greater reporting of benefits on symptoms.
- For subjects taking 300 mg, significant favorable and unfavorable effects of symptoms were observed.
- Digital span backward cognitive test—no effects observed, but poor sensitivity to self-ratings.

PHASE I/II COQ10 STUDY RESULTS
COQ10 BLOOD LEVELS

- Some participants who took 100 mg or 300 mg failed to show increases in CoQ10 levels.
- Largest CoQ10 increases seen in the group taking 300 mg.
- At least 1 participant in Placebo group showed a sizeable increase.
- The largest CoQ10 increase in Placebo group exceeded the largest CoQ10 increase in Q100 group.
- Some subjects who took higher dose of 300 mg did not change their CoQ10 levels nor their outcomes by a large amount.
- Some subjects who took 300 mg and who increased their CoQ10 levels had no ability to change their outcomes since their baseline scores on the general health scales were at the top score.

PHASE I/II AND PHASE III COMPARISON: PRESCRIPTION AND DISPENSING

Comparative Indicator	Phase III—New	Phase I / II
Number of VA Sites Involved	4 -- FL, MA, MN, NY	1 -- California
Total number of Research Participants	200	46
Form of CoQ10:	Ubiquinol	Ubiquinone
Prescription dosage and # participants	100 Ubiquinol 200 mg 100 Placebo	11 Ubiquinone 100 mg 12 Ubiquinone 300 mg 23 Placebo
Drug Dispensing	1 softgel for 4 months 2 softgels for 2 months Taken once/day	3 softgels: 1 larger + 2 smaller Taken 3 times/day
Timing of dose	Morning only	Morning, afternoon, evening
Outcome Measures	Medical Outcomes SF-36 3 Cognitive Tests: Several validated survey tools Biomarkers	General Self0-Rated Health 1 Cognitive Test: Digital Span backwards General survey (not validated) Biomarkers

IMPORTANCE OF COENZYME Q10

- Coenzyme Q10 exists in our cells and facilitates the transformation of fats and sugars into energy.
- When CoQ10 levels lower, the ability of cells to sustain energy is impaired.
- Scientific evidence shows that CoQ10:
    - Provides benefits to organs whose cells require high-level energy demands such as the heart, brain, and kidneys
    - Has the ability to restore function
    - Has a beneficial effect on overall health.
- CoQ10 levels can be fully restored by taking the proper dose of supplemental CoQ10.

TWO MAIN FORMS OF CoQ10

Ubiquinone
Phase I/II

Ubiquinol
Phase III

To gain the benefit, our bodies must convert Ubiquinone into Ubiquinol before it can be used to create cellular energy.

Both are present within the body's cells and both are needed to generate and maintain cellular energy.

COMPARISON OF TYPES OF COQ10

- **Ubiquinol is superior to Ubiquinone:**
    - Maintains higher CoQ10 blood levels longer
    - Is 8 times **more absorbable**
    - Provides superior health benefits
- CoQ10 blood levels are 60% higher after taking only 1 dose of ubiqui**nol** compared to Ubiqui**none**.
- Ubiqui**none** is:
    - More well-known and was taken as a supplement during the past 30 years because ubiquinol was not available as a supplement until 2006.

COQ10 UBIQUINOL PHARMACOKINETICS

- **Bioavailability:** Absorption is slow and limited. Food may enhance bioavailability.
- **Metabolism:** Hepatic, but can occur within all tissues
- **Half-life elimination:** 33-48 hours
- **Time to peak, serum:** 5-10 hours first peak; 24 hours second peak (enterohepatic recirculation)
- **Conc. steady state:** 2 weeks
- **Excretion:**
  - Major: Biliary and fecal excretion
  - Minor: Urinary

COMPARISON OF PHASE I/II AND PHASE III CLINICAL TRIALS

Comparative Indicator	Phase III—New	Phase I / II
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PHASE III CLINICAL T
RESEARCH DESIGN

- Randomized, Double Blind, Placebo controlled
- Multi-site Study at 4 VA Medical Centers (VAMC)
- Total Participants= 200 50 veterans from VAMC
- 25 Active CoQ10 and 25 Placebo at each VAMC
- Comparison of Group A and Group B
- Comparison of Response Rate across 3 assessment times

PHASE III CLINICAL TRIAL RESEARCH OBJECTIVES

Objectives:

- To determine the efficacy of CoQ10 in GWI related symptom control
- To evaluate putative biomarkers for their ability to predict severity and response to therapy
- To test the utility of measures of illness severity and function as outcome variables in GWI.

PHASE III CLINICAL TRIAL SPECIFIC AIMS

- Perform a randomized, double blind, placebo control, Phase III study comparing CoQ10 (ubiquinol) to placebo, with a 6 month intervention and assessment of safety, efficacy and biomarker response to therapy;
- Perform biomarker studies before and after 2, 4, and 6 months of therapy, with blood and saliva collections, hormone studies, and laboratory assessments.
- Assess the domains of illness and illness severity, and evaluate the utility of the selected instruments for future clinical trials use in GWI.

PHASE III CLINICAL TRIAL
BIOREPOSITORY

- Housed at Miami VA Healthcare System
- Future Analyses include:
  - NK cell cytotoxicity
  - Flow cytometry
  - Plasma cytokines
  - Thiol
  - Mitochondrial function
  - Gene expression

Newly funded CDMRP grant will support the mechanisms project (Fletcher, PI, Klimas partner PI)

PHASE III CLINICAL TRIAL PRIMARY OUTCOME VARIABLE

Medical Outcomes Study 36-item Short-Form Health Survey (SF-36)

A general indicator of health status (function and well-being) with physical and emotional subscales.

Study Focus: Physical Subscale

The SF-36 assesses health-related quality of life in 8 areas:

1.) Limitations in physical activities because of health problems
2.) Limitations in social activities because of physical problems;
3.) Limitations in usual role activities because of physical health problems
4.) Bodily pain
5.) General mental health;
6.) Limitations in usual role activities because of emotional problems
7.) Vitality (energy and fatigue);
8.) General health perceptions

PHASE III CLINICAL TRIAL SECONDARY OUTCOME VARIABLES

- **Composite International Diagnostic Interview (CIDI**): Computer driven interview format assessment to diagnose current and lifetime DSM-IV Axis 1 psychiatric disorders. These include mood, anxiety, psychotic, substance abuse, eating and somatoform disorders.
- **GWI Health Symptom Checklist (HSC),** a list of the domains noted in the GWI case definitions (previously determined by factor analysis), with a visual analog severity scale, including current, worst day and best day scales which we have further adapted to include frequency of symptom.
- **Multidimensional Fatigue Inventory (MFI)** s a 20-item self-report instrument designed to measure fatigue. It covers the following dimensions: General fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity.

PHASE III CLINICAL TRIAL
SECONDARY OUTCOME VARIABLES

- **Pittsburgh Sleep Inventory** (short form) measuring quality of sleep.
- **Ham-D, Ham-A** measuring depression and anxiety.
- **Davidson Trauma Scale** assesses symptoms of PTSD in three clusters: intrusion, avoidance, and hyperarousal. While not exclusion criteria unless hospitalized for PTSD in the prior 3 years, this information is collected to establish subpopulations and inform the understanding of results.
- **Fitbit** counts heart rate, steps, stairs, periods of inactivity, that can tabulate this indirect measure of hours of sleep, restless periods of sleep, awake periods during sleep, and naps.
- **Gynecologic Questionnaire** assesses routine gynecologic parameters and time of assessment as it relates to menstrual cycle.

PHASE III CLINICAL TRIAL
SECONDARY OUTCOME VARIABLES

- **Autonomic nervous system measures** includes measurement of blood pressure and heart rate in laying and standing positions. Subjects are recumbent for 30 minutes and stand for five minutes and ten minutes. Blood pressure and heart rate are measured at lying and after five and ten minutes of standing.
- **Pain** assessed using a 10-cm visual analog scale, in which 0 = no pain and 10 = the worst pain possible. Note that the PE also includes a quantitative tender point evaluation.
- **Biomarkers**

PHASE III CLINICAL TRIAL SECONDARY OUTCOME VARIABLES: COGNITIVE MEASURES

- **Conners Continuous Performance Test** (CPT-3) is a test of attention, vigilance, and tracking of reaction time total omission and commission.
- **California Verbal Learning Test** (CVLT-II) is a test of learning strategies and visual memory.
- **Brief Visual Memory Test** (BVMT) measures visual memory total recall

PHASE III CLINICAL TRIAL RECRUITMENT CONCERNS

- Primary Care Outpatient Setting
- Local Site Gulf War Registry List
- National Gulf War Registry List
- CSP 585 collaboration

  Veterans who had a mandated exam and opt in:

  - Initial contact by mail
  - Follow-up via telephone, screening by the Registry Recruiter based at the Miami VA

PHASE III CLINICAL TRIAL ELIGIBILITY CRITERIA

- Veterans between 35 and 70 years old
- Good health by medical history prior to 1990
- Not have exclusionary diagnoses that could reasonably explain the symptoms of fatigue and severity

PHASE III CLINICAL TRIAL ELIGIBILITY CRITERIA

- Meet Kansas Case Definition
- Deployment to the theater of operations between August 8, 1990 and July 31, 1991
- Multiple and moderately severe symptoms (> 6 months) in at least 3 of 6 symptom domains
    - Fatigue/sleep problems
    - Somatic pain symptoms
    - Neuro/cognitive/mood symptoms
    - Gastrointestinal symptoms
    - Respiratory symptoms
    - Skin symptoms

PHASE III CLINICAL TRIAL EXCLUSION CRITERIA

Psychiatric Conditions:

- Major depression with psychotic or melancholic features
- Schizophrenia
- Bipolar disorder
- Delusional disorders
- Dementias of any type
- Alcoholism or drug abuse
- Hospitalization in past 6 months for Post-traumatic stress disorder (PTSD)

PHASE III CLINICAL TRIAL EXCLUSION CRITERIA

Medical conditions:

- Auto-immune disease (lupus, defined rheumatologic inflammatory disorders)
- Organ failure
- Chronic active infections such as HIV, hepatitis B and C
- Transplant
- Primary sleep disorders
- Pregnancy

PHASE III CLINICAL TR
EXCLUSION CRITERIA

Medications that could potentially impact immune function:

- Steroids
- Immuno-suppressives
- Nutraceuticals that are formulated to impact mitochondrial function or oxidative stress
- Morphine derivatives that are used daily
- Known allergy to CoQ10 and/or inactive ingredients of active and placebo soft gelatin capsules
- Current use of Coumadin (given the vitamin K structural similarity of CoQ10)

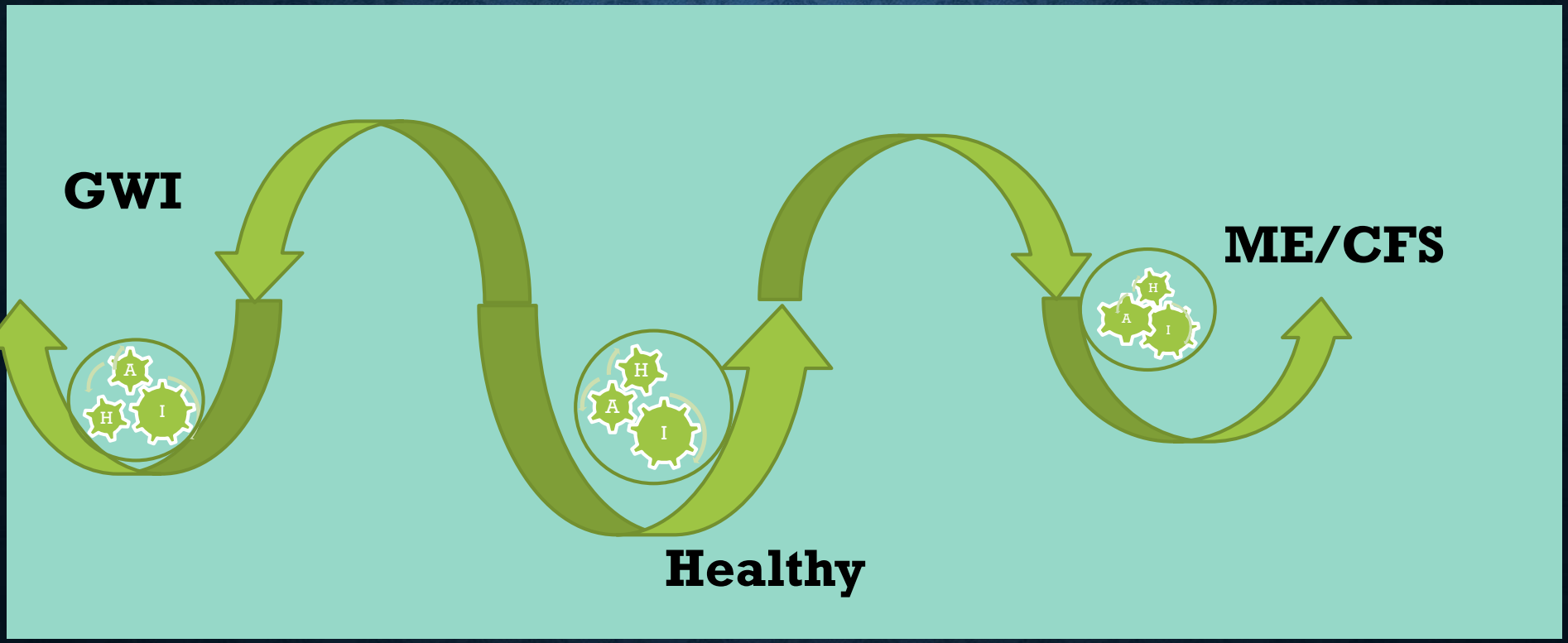
PHASE III CLINICAL TRIAL CONDITIONS AND MEDICATIONS NOT EXCLUDED

- Infectious disease or medical condition apparent at the screening visit, the subject will be counseled and referred to primary care.
- Occasional use of less strong pain medications such as tramadol or codeine (monitor for frequency of use as an indication of CoQ10's impact on chronic pain).
- Common multivitamin preparations will be allowed if taken without change throughout the protocol.
- Wash-out period of 12 weeks prior to study entry is required for CoQ10 or other nutraceuticals formulated to impact mitochondrial function.
- **Agreement to leave any medications and other supplements unchanged in their regimen throughout the course of the 6 month intervention.**

PHASE III CLINICAL TRIAL TIMELINE

Year 1	• **Staff Training** • **IRB Approval Process** • **Begin Recruitment**
Year 2	▪ **Recruitment** ▪ **Data Collection**
Year 3	▪ **End Recruitment and Data Collection** ▪ **Data Analysis** ▪ **Dissemination of Findings**

HOMEOSTATIC IMBALANCE



EXERCISE CHALLENGE TO MAP OUT MECHANISMS OF RELAPSE

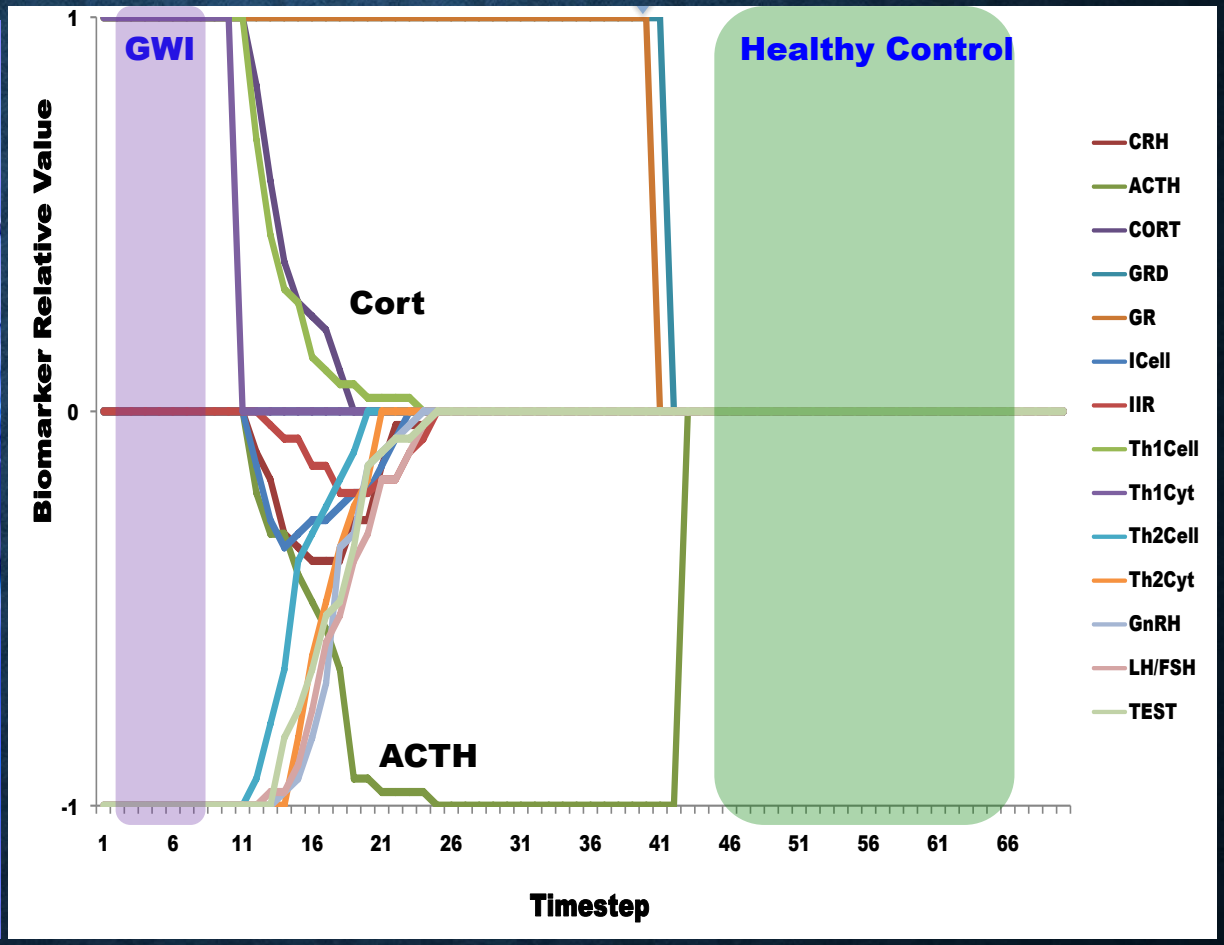
NSU NOVA SOUTHEASTERN UNIVERSITY College of Osteopathic Medicine

INIM Institute for Neuro-Immune Medicine

Treatable:
Delivering lasting remission

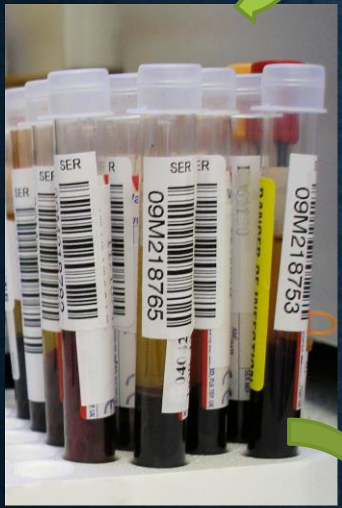
Th1 inflammatory Cytokine Inhibition (e.g.TNFa)

Gluccocorticoid Receptor Inhibition



Integrating basic science with clinical data…

one-two endocrine-immune punch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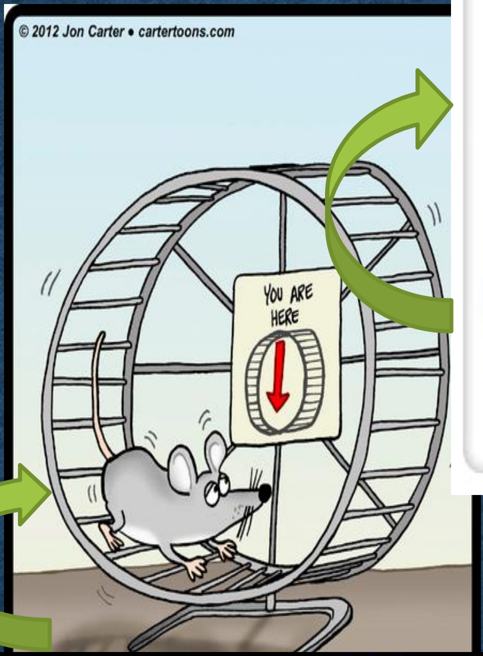
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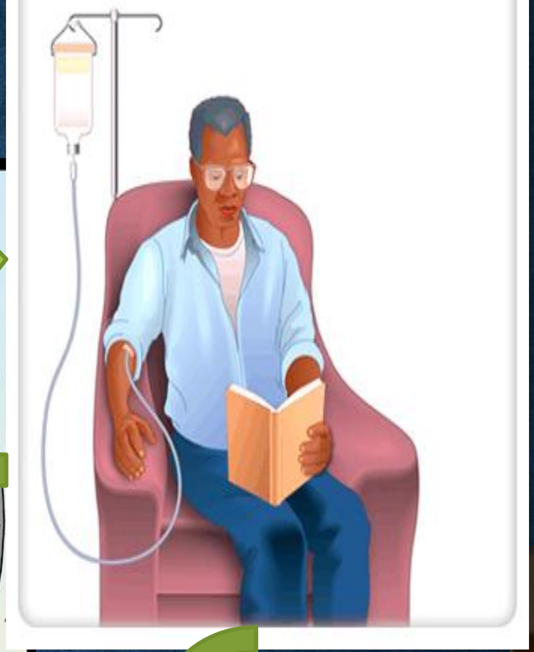


CHAOS
CHANGE
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COMPLEXITY
HAPPENSTANCE
GROWTH
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IMAGINING
DISRUPTING
OPPORTUNITY DISORDER
PHASE-SHIFT
EXPERIMENTING
VULNERABLE
CONSTRUCTIVIST
RE-THINK
OPEN-MINDED
BREATHING
EXCITEMENT
PARTICIPATE
ENGAGEMENT
FLEXIBLE
IRREGULAR
DYNAMIC
AMAZING
ABANDON
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AMBIGUITY
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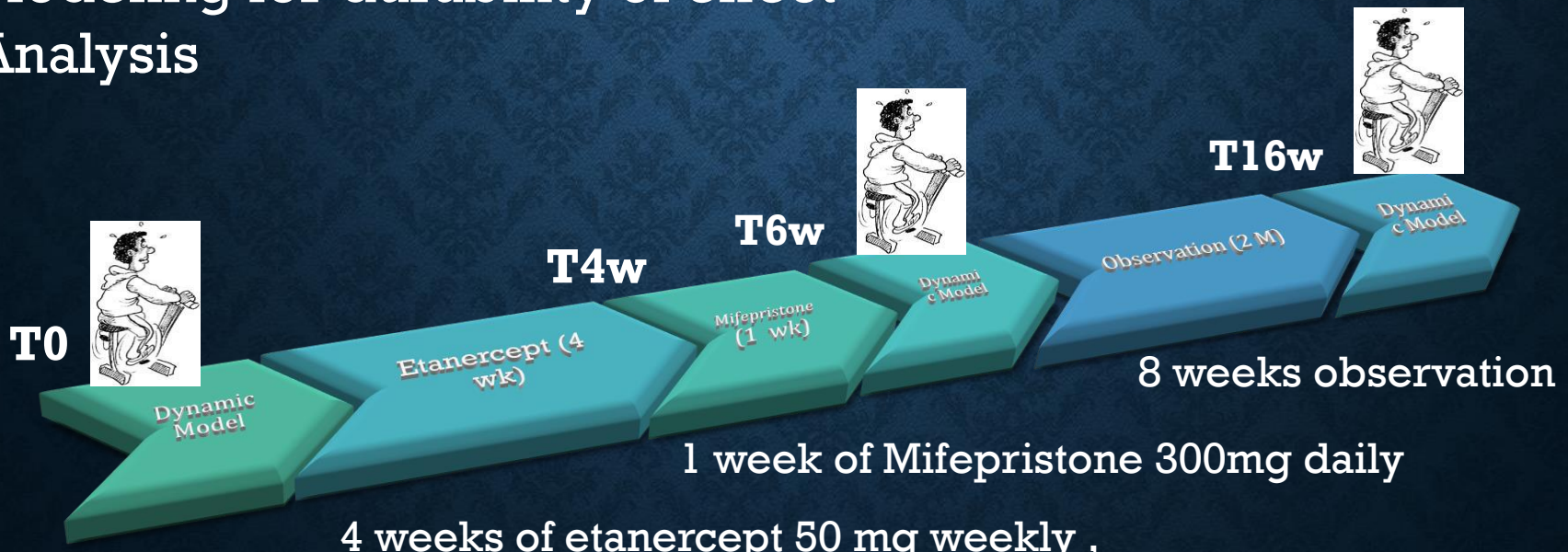
JAZZ
CONFOUNDING
LUCKINESS
MOVEMENT
INQUIRE
PUPPYISH
PADDLE
MUTABLE
OPEN
AMENABLE
ACTUALIZING
DYNAMICAL
@JINBRIGHT2012

PHASE I PROOF OF CONCEPT TRIAL (NSU GWIC)

Baseline challenge for modeling
Intervention 4 weeks etanercept, then 1 week mifepristone
Post treatment challenge for modeling
2 month observation
Modeling for durability of effect
Analysis



8 weeks observation

1 week of Mifepristone 300mg daily

4 weeks of etanercept 50 mg weekly ,

Recruitment 20 subjects over 12 months, complete in 16 months

NFKB TARGETING – COMPUTATIONAL MODEL

- Phase 2 placebo control trial comparing two nutraceuticals:
- Curcumin
- Liposomal glutathione
- Involves using the exercise challenge to look at regulatory balance, 4 month intervention, then repeat challenge
- Determine if targeting NFKb impacts downstream events (TH1/TH2, NK function , proinflammatory cytokine expression)

CONCLUSION

- Targeting mediators of illness persistence teaches us much about the underpinnings of illness, and can be used to test the models in addition to the primary goal: restoring veterans with GWI to health
- Our group has 4 active clinical trials, with additional studies for specific subgroups ready to roll out.
- Thanks to robust funding mechanisms, the current biggest barrier to delivering effective therapy to our veterans is accessing veterans willing to volunteer in these studies. An effective partnership with veterans organizations with this goal in mind could deliver effective treatments far sooner.

ME/ CFS
Gulf War Illness

- Identifiable
- Treatable
- New treatments will follow new understanding

THE INIM TEAM

INIM Administration

Nancy Klimas– Director
Ana Del Alamo– Administrative Director
Nilda Hernandez –
Kerline Geffrard – clinics manager
Anabel Cabrera
Tramiel Dillard
David Freeman
Melanie Perez

Clinical Team

Nancy Klimas, MD
Irma Rey, MD
Maria Vera, MD
Alison Bested, MD
Violetta Renesca. ARNP
Irina Rozenfeld, ARNP
Jeff Cournoyer, Exercise Physiologist
Elaine Burricaudy
Annette Green

Immunology /Biomarkers

Mary Ann Fletcher – Director
Lubov Nathanson ,PhD
Paula Waziry , PhD
Kristina Aenlle, PhD
Maria Abreu, PhD
Xiao Rong Zeng, PhD
Zach Barnes, manager
Lissette Pierlus
Howard Lin
Claudia Vizcarra
Gilbert Eugene
Sandra Yudice
Zachary Barnes
Bisha Chen

Animal Research

Mariana Morris – Director
Aman Cheema
Jaqueline Machi
Rodrigo Schmidt

Clinical Systems Biology

Gordon Broderick (RU) - Co Director
Travis Craddock – Co-Director
Mark Rice
Patrick Gourdet
Tory Toole
Mary Jeffrey
Rajeev Jaundoo
Saurabh Vashishtha
Lindsey Russell
Trevor Barker
Gaytri Patel

Clinical Research

Nancy Klimas, MD director
Elizabeth Balbin –Manager
Kelly Hilton , CC2
Devra Cohen
Precious Leaks-Gutierrez
Fanny Collado
James Blount

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INIM TEAM

- *Mission: Advance knowledge and care for people with complex neuro-inflammatory illnesses through the integration of research, clinical care and education*

MORE INFORMATION

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Questions and Concerns