TISSUE FACTOR
and
GULF WAR-ASSOCIATED CHRONIC COAGULOPATHIES

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VA FUNDING

- **"Tissue Factor and Gulf War-Associated Chronic Coagulopathies"**
  VHA ORD Request for Proposals:
  Research Directed to Understanding Illnesses Affecting Gulf War Veterans
  (04/01/2006 to 03/31/2008)

- **"Gulf War-Associated Chronic Coagulopathies: Tissue Factor, Coagulation, and Immune System Activation"**
  Service-Directed Gulf War Supplemental Project
  (04/01/2008 to 9/30/2009)

STUDY GOAL

Identify biomarkers
specific for
Gulf War Illness (GWI)

BACKGROUND:

BLOOD COAGULATION & GWI

- **Previous work has suggested the possibility of a hyperactive coagulation system in veterans with GWI.**

  (Blood Coagulation & Fibrinolysis, 2000, 11:673-678)

- **What could cause such a coagulopathy?**

BACKGROUND:

WHAT INITIATES BLOOD CLOTTING?

- **Tissue factor (TF) is the biological initiator of blood coagulation.**
- **Expression of TF procoagulant activity (PCA) is essential for normal hemostasis.**
- **Abnormal expression of TF PCA is a trigger for thrombosis: heart attacks, strokes, and disseminated intravascular coagulation.**

STUDY PARTICIPANTS:

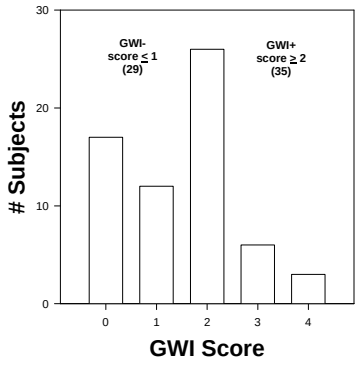
MN Veterans of the Gulf War

(Operations Desert Shield and Desert Storm: August 2, 1990-July 31, 1991)

■ Recruitment:	Randomly selected from the Persian Gulf War Registry
■ Enrollment rate:	15%
■ # Subjects :	64
■ Sex:	89% Male (57) 11% Female (7)
■ Age:	47.8±9.5 years
■ Age Range:	36-72 years

GWI SCORING
(chronic symptoms)

- Fatigue
- Pain
- Inflammation
- Cognitive Problems



BLOOD ANALYSIS I:
Intravascular TF PCA

- Purify monocytes and platelets from EDTA-anticoagulated blood.
- Quantify the TF PCA associated with isolated monocytes and platelets in a clot-based functional assay.

BLOOD ANALYSIS II:

Coagulation End-Products

(Plasma Levels Determined by ELISA)

- Thrombin-Antithrombin Complex
- D-dimer (a degradation product of cross-linked fibrin)

CONCLUSIONS

- The increase in platelet$^{TF\ PCA}$ coupled with the decrease in monocyte$^{TF\ PCA}$ is **indirect evidence** of coagulation system activation in the GWI+ group.
- The higher level of thrombin-antithrombin complex is **direct evidence** of coagulation system activation in the GWI+ group.
- Both results support the hypothesis that GWI is a hypercoagulable state.

BLOOD ANALYSIS III:

Proteomics Screen for Additional Plasma Proteins Abnormalities

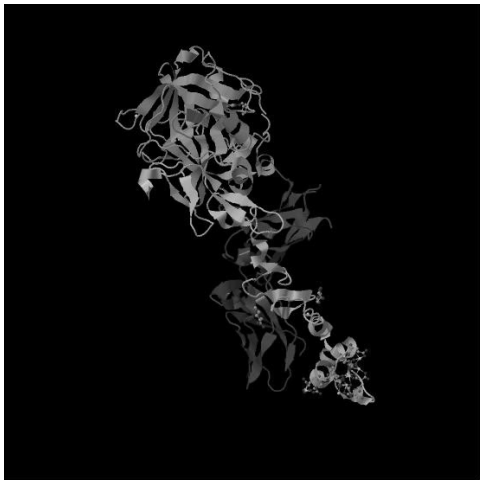
- Quantify plasma levels of 89 antigens with a focus on inflammation-related proteins.
- Analyses were performed by:
  Rules Based Medicine, Austin TX.

RBM HumanMAP® Antigens, version 1.6

- Adiponectin
- Alpha-1 Antitrypsin
- Alpha-Fetoprotein
- Alpha-2 Macroglobulin
- Apolipoprotein A-1
- Apolipoprotein C-III
- Apolipoprotein H
- Beta-2 Microglobulin
- BDNF
- C-Reactive Protein
- Calcitonin
- Cancer Antigen 19-9
- Cancer Antigen 125
- Carcinoembryonic Antigen
- CD40
- CD40 Ligand
- Complement 3
- CK-MB
- Endothelin-1
- Eotaxin
- Epidermal Growth Factor
- ENA-78
- Erythropoietin
- ENRAGE
- Factor VII
- Fatty Acid Binding Protein
- Ferritin
- Fibrinogen
- FGF-basic
- GST
- G-CSF
- GM-CSF
- Growth Hormone
- Haptoglobin
- Immunoglobulin A
- Immunoglobulin E
- Immunoglobulin M
- Insulin
- IGF-1
- ICAM-1
- Interferon-gamma
- Interleukin-1 alpha
- Interleukin-1 beta
- Interleukin-1 ra
- Interleukin-2
- Interleukin-3
- Interleukin-4
- Interleukin-5
- Interleukin-6
- Interleukin-7
- Interleukin-8
- Interleukin-10
- Interleukin-12 p40
- Interleukin-12 p70
- Interleukin-13
- Interleukin-15
- Interleukin-16
- Leptin
- Lipoprotein (a)
- Lymphotactin
- MDC
- MIP-1 alpha
- MIP-1 beta
- MMP-2
- MMP-3
- MMP-9
- MCP-1
- Myeloperoxidase
- Myoglobin
- PAI-1
- PAPP-A
- PSA, Free
- Prostatic Acid Phosphatase
- RANTES
- Serum Amyloid P
- SGOT
- Sex Hormone Binding Globulin
- Stem Cell Factor
- Thrombopoietin
- Thyroid Binding Globulin
- Thyroid Stimulating Hormone
- Tissue Factor
- TIMP-1
- Tumor Necrosis Factor-alpha
- Tumor Necrosis Factor-beta
- Tumor Necrosis Factor RII
- VCAM-1
- VEGF
- von Willebrand Factor

COAGULATION FACTOR VII

TF-FVIIa COMPLEX
(INITIATOR OF BLOOD COAGULATION)



CONCLUSIONS

- Most subjects enrolled in this study had abnormally high levels of thrombin-antithrombin complex, D-dimer, and factor VII antigen.

- These unusual coagulation system parameters may represent a heretofore unknown state of

Compensated Chronic

Disseminated Intravascular Coagulation.

QUESTIONS

- Is GWI a cause or an effect of the observed hypercoagulability?

- Why is the frequency of coagulation parameter abnormalities so high in this study population?

FUTURE GOAL

Translating GWI-Specific Biomarkers into Clinical Practice:

1. Diagnose GWI with blood tests.

2. Evaluate the efficacy of potential therapies.