“Chronic Fatigue Syndrome (CFS) or Myalgic Encephalomyelitis (ME)”

Jose G. Montoya, MD, FACP, FIDSA,
Professor of Medicine, Stanford University
Director, Palo Alto Medical Foundation Toxoplasma Serology Laboratory
Palo Alto, CA
• Measles, EBV, Dengue, Chikungunya, MERS-CoV, Ebola

• viruses link to cancer

• can viruses trigger or sustain chronic unexplained illnesses such as CFS/ME
  – clinical case/what is it
  – epidemiological data
  – biological plausibility
  – clinical observations and trials
Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is a real illness that devastates the lives of millions of people in the United States and worldwide.

- “Patrick” is a scientist who was at the peak of his research endeavors, working on an animal model to determine the relationship between HHV-6 and CFS/multiple sclerosis. P119 was having the time of his life with a successful career and beautiful family.
- Summer of 2006 developed worst GI illness.
- Fall of 2006 developed severe fatigue, cognitive difficulties, profuse sweats, chills, 60 lbs weight loss, fluctuating personality changes and memory loss, sleeplessness, daily hypersomnia, right leg weakness and brain stem signs.
- Extensive evaluations ruled out early dementia, malignancy and treatable causes of encephalopathy.
Patient developed a highly fluctuating illness consistent with full blown ME/CFS and serious neurological signs

• early and at the peak of patient’s illness, was found to have by PCR, HHV-6A DNA in blood (1 x 10^6 copies/ml) and weeks later in cerebrospinal fluid (~1,200 copies/ml) with subsequent negative tests

• at the same time MRI T2-W bright lesions in right thalamus and internal capsule

• patient remained very fatigued and unable to perform at high levels at work

• was seen at Stanford, placed on valganciclovir, and had a significant clinical response
**HHV-6 PCR in peripheral blood**

**Around the time symptoms were worse**

Results are presented in duplicate.

Extreme Left: Molecular markers ladder.

The bands at 265 bp represent PCR amplification of HHV-6A DNA extracted from P119’s whole blood (arrows).

HSB2/HHV-6A: Positive control (265 bp); MOLT3/HHV-6B: Positive control (361 bp).

These PCR reactions are performed in the same tube and distinguish the two variants very clearly.

H2O: Negative control.
Coronal FLAIR and Axial T2-Weighed lesion involving the Right Thalamus and Posterior Limb of the Internal Capsule
One of the biggest mistakes made by modern medicine is to have arrived to the conclusion that diseases such as CFS, FM, GWI, and CLD are psychological in origin

- experienced by a significant number of patients whose lives have been devastated by its symptoms

- there are no diagnostic tests that can identify with certainty these patients

- a definitive treatment is not available except for some patients with CLD in whom it can be demonstrated that *Borrelia burgdorferi* is actively triggering the illness

- some patients spontaneously improve with time but most remain functionally impaired for several years
Diagnostic Challenges

Fatigue and other symptoms are common to many other illnesses.

For some patients, it may not be obvious to health care providers (and to some family members!) that they are ill.

Pattern of remission and relapse.

Symptoms vary from person to person in type, number, and severity.

Diagnosis based on medical history, illness symptoms, physical examination, and exclusion of certain illnesses using a standard group of laboratory tests.

Low diagnosis rate since there’s no lab test or biomarker.
### Clinical Diagnosis of CFS/ME by Fukuda Criteria

<table>
<thead>
<tr>
<th>Chronic Fatigue Syndrome Criteria</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the patient have fatigue for ≥ 6 months?</td>
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<tr>
<td>2. Does the patient meet the criteria for severity of fatigue? (YES to a-d below)</td>
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<tr>
<td>a. Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or</td>
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<td>definite onset (i.e., not life-long)</td>
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<td>b. Fatigue is not the result of ongoing exertion</td>
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<td>c. Fatigue is not substantially alleviated by rest</td>
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<td>d. Fatigue results in substantial reduction in previous levels of occupational, educational,</td>
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<td>social, or personal activities</td>
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<tr>
<td>3. Does the patient have ≥4 of the following for ≥6 months?</td>
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<tr>
<td>a. Impaired memory or concentration</td>
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<tr>
<td>b. Sore throat</td>
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<tr>
<td>c. Tender cervical or axillary lymph nodes</td>
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<tr>
<td>d. Muscle pain</td>
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<tr>
<td>e. Multi-joint pain</td>
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<tr>
<td>f. New headaches</td>
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<tr>
<td>g. Unrefreshing sleep</td>
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<tr>
<td>h. Post-exertional malaise</td>
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<tr>
<td><strong>If YES to ≥4, then:</strong> Meets clinical criteria for chronic fatigue syndrome (CFS) diagnosis (see</td>
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<td>ICFSSG, 1994)</td>
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</table>

*We can provide the Fukuda criteria to Stanford clinicians as a “Smart phrase” in EPIC*
Demographic and socioeconomic profile of ME/CFS patients

- Mid-30’s (5-65)
- 65% female
- Middle-class, but more common African-American/Latino minority populations on population-based surveys
- 50% college graduates in office-based samples
- 50% intermittently bedridden/shut-in
- 14 years (4-36)
For the past 33 years well conducted research has provided evidence that CFS/ME is a condition that is often triggered by an infection leading to a neuro-inflammatory process

- Sudden/infectious onset
- Chronic activation of the immune system
- Hypothalamic-pituitary axis abnormalities
- Significant cognitive difficulties not explained by psychiatric disorders
- Autonomic dysfunction
- MRI/SPECT/EEG abnormalities
It has been demonstrated that CFS can be precipitated by an acute and severe infection.
Observations on the pathogens that have been typically associated with CFS

- most if not all the pathogens that have been associated with the onset of CFS are intracellular

- in addition to their intracellular state they appear to share certain initial tropism (e.g. respiratory, gastrointestinal) followed by subsequent preferential target organs (e.g. CNS, lymphopoietic system)
Several pathogens have been reported to have the capacity to "trigger" CFS:

- This observation suggests that most likely it is the immune response against them that is responsible for the patients' symptoms.
- Immune response to different intracellular pathogens has common pathways regardless of the organism.
- Subgroups of CFS patients (e.g., "clinical clusters") may arise from the primary entry site.
<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Disease</th>
<th>Humoral immunity</th>
<th>Cell-mediated immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IgM</td>
<td>IgG</td>
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<tr>
<td><strong>Viruses</strong></td>
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<tr>
<td>Herpes zoster</td>
<td>Chickenpox</td>
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<tr>
<td>Epstein–Barr virus</td>
<td>Mononucleosis</td>
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<tr>
<td>Influenza virus</td>
<td>Influenza</td>
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<tr>
<td>Polio virus</td>
<td>Poliomyelitis</td>
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<tr>
<td><strong>Intracellular bacteria</strong></td>
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<tr>
<td><em>Rickettsia prowazekii</em></td>
<td>Typhus</td>
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<tr>
<td>Mycobacteria</td>
<td>Tuberculosis, leprosy</td>
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<td></td>
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<tr>
<td>** Extracellular bacteria**</td>
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<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Boils</td>
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<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Pneumonia</td>
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<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Meningitis</td>
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<tr>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Diphtheria</td>
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<tr>
<td><em>Vibrio cholerae</em></td>
<td>Cholera</td>
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<tr>
<td><strong>Fungi</strong></td>
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<tr>
<td><em>Candida albicans</em></td>
<td>Candidiasis</td>
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<tr>
<td><strong>Protozoa</strong></td>
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<tr>
<td><em>Plasmodium spp.</em></td>
<td>Malaria</td>
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<td><em>Trypanosoma spp.</em></td>
<td>Trypanosomiasis</td>
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<td><strong>Worms</strong></td>
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<tr>
<td>Schistosome</td>
<td>Schistosomiasis</td>
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Figure 10-16 Immunobiology, 7ed. (© Garland Science 2008)
CFS is sustainable for several years or even decades and typically causes a fluctuating illness

- the pathogen(s), concomitantly or sequentially, must be reactivating periodically (thus, ongoing but fluctuating symptomatology)

- reactivation must be at low levels

- the pathogen(s) must reactivate at a level enough to trigger an immune response with a “double-edge sword:
  - "sending back" the pathogen to a temporal state of latency
  - causing symptoms
CFS is more common in women, often gets better during pregnancy but worsens after birth, has been associated with presence of autoantibodies

- suggests autoimmunity

- HLA association
Immune abnormalities in CFS patients that appear to be more consistently reported across laboratories

- NK cell activity decreased
- CD3-/CD56+ NK phenotype decreased
- CD4/CD45RA % decreased
- Antinuclear antibody positivity increased
- Th2 proclivity?

How did Stanford get involved in chronic fatigue syndrome?

As a response to the suffering experienced in solitude by millions of patients who have patiently waited for an answer from the medical and scientific research communities, an infectious trigger and perpetuator is likely.
Can we make unexplained illnesses such as CFS/ME and CLD treatable and curable conditions?

José G. Montoya, MD
Professor of Medicine
Division of Infectious Diseases
Stanford University School of Medicine
Institute of Immunity, Transplantation, and Infection
Human Immune Monitoring Center
Mark Davis, PhD
Holden Maecker, PhD
Yael Rosenberg-Hasson
Rosemary Fernandez
Xuhuai Ji
Janine Sung

Immunology and Rheumatology
William Robinson, MD

Department of Genetics
Ron Davis, PhD
Michael Mindrinos, PhD
Wenzhong Xiao, PhD
Amit Kaushal, MD, PhD
Weihong Xu, PhD

Department of Bioengineering
Stephen Quake, PhD
Michael Kertesz, PhD

Columbia University Center for Infection and Immunity
Ian Lipkin, MD; Mady Hornig, MA, MD

Department of Anesthesia
Jared Younger, PhD

Neuroradiology
Michael Zeineh, MD-PhD

Cardiology
Francois Haddad, MD

General Medical Disciplines
Mehdi Skhiri, MD

Department of Psychiatry
Jose R. Maldonado, MD

Department of Statistics
Tyson Holmes, PhD
Lily Chu, MD, MS
Advisory Board Member: International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis
Patient advocate

Mark Davis, PhD
Professor of Microbiology and Immunology - Stanford University
Director: Institute for Immunity, Transplantation and Infection - Stanford University

Dennis Mangan, PhD
Director, Chalk.Talk.Sciences Educational Services - Researchers Communicating Science to the Public
Advisor, IACFS/ME - non-profit international Chronic Fatigue Syndrome professional organization
Former: Health Scientist Administrator/Program Director, National Institutes of Health (NIH);
Advisor to the NIH Director on Chronic Fatigue Syndrome; Chair, Trans-NIH Chronic Fatigue Syndrome Research Working Group
Associate Dean for Research, University of Southern California School of Dentistry

Margaret Raffin
Immediate past chair: Palo Alto Medical Foundation Community Board
President: Ishiyama Foundation

Thomas Raffin, MD
Emeritus professor: Stanford Medical School
Partner: Telegraph Hill Partners

Abraham Verghese, MD, MACP
Professor of Medicine
Senior Associate Chair for the Theory and Practice of Medicine
Member, Institute of Medicine, National Academy of Sciences
Stanford ME/CFS team

José G. Montoya, MD Professor of Medicine in the Division of Infectious Diseases

Marcie Zinn, PhD Neuropsychologist

Aimee Jadav, PA-C Physician Assistant

Ian Valencia, BS Study Coordinator

Jane Norris, PA-C Study Coordinator

Diana Dobbs, BS Clinical Research Assistant

Steven Smallberg, BA Clinical Research Assistant

Mark Zinn, MM, PC

Amity Hall, PA-C Physician Assistant
Study designs at Stanford in CFS patients

• Randomized, double-blind, placebo controlled clinical trials

• Longitudinal studies (Jared Younger, PhD)

• Case-control studies
  • 200 CFS patients vs 400 healthy controls
  • Department of Genetics and Genome Technology Center (M. Mindrinos, R. Davis, W. Xiao)
    – Gene expression, HLA

• Stanford HIMC
  – 51-multiplex cytokine analysis
  – Inflammatory gene expression
  – CyTOF platform
  – Antibody repertoire (W. Robinson)

• Center for Infection and Immunity (I. Lipkin)
  • MassTag-PCR, deep sequencing

• Clinical characteristics of CFS/ME patients

• Additional hypothesis generating studies
  • Brain Electrical activity (EEG)
  • Brain anatomy and function (MRI)
  • Cardiac and endothelial function in the setting of PEM
Circulating cytokine profile in CFS patients by illness severity
Thirteen cytokines were identified as having an upward trend when analyzed by progression in CFS severity

- CCL11, CXCL1, CXCL10, GM-CSF, IFN-γ, IL-4, IL-5, IL-7, IL-12P70, IL-13, IL-17F, leptin, and LIF

- cell trafficking
  - eosinophil, basophil, and mast (CCL11); neutrophil (CXCL1)

- cell activation
  - B cell (IL-4, IL-7, IL-13, CD40); NK cell (IL-12), macrophage (CD40)

- cell growth and differentiation
  - pre-T cells (IL-7); myelomonocytic lineage cells particularly dendritic cells (GM-CSF); eosinophil (IL-5)

- enhancement of macrophage activity (leptin)

- maintenance of embryonic stem cells (LIF)

- increased MHC class I expression (IFN-γ)

- cytokine production by epithelia, endothelia and fibroblasts (IL-17)

- Th1 response (CXCL10, IL-12), Th2 response (IL-4, IL-13)

- adipocyte cytokines pro-inflammatory: leptin and resistin
Colocalization of DTI and Cortical Thickness Differences

Right arcuate (blue tracks and arrow) and inferior longitudinal fasciculi (yellow tracks and arrow) in a single representative subject. These two tracks are overlaid upon their respective track profiles (the centroid of each track averaged across subjects, depicted as the large tubular structures at the core of each track). The track profile is colored according to the T-score (0-4) of track-based fractional anisotropy (FA), showing the maximal increase in FA is in the anterior arcuate and inferior longitudinal fasciculi. The red, blue, and green spheres correspond to size and locations of increased cortical thickness in the right occipital, precentral, and middle temporal regions, respectively. The green arrow also points to the middle temporal region of increased thickness.
Herpes viruses are ubiquitous, infect as significant proportion of individuals and establish life-long latency.

<table>
<thead>
<tr>
<th>HHV subfamilies</th>
<th>Serial Arabic number designation</th>
<th>Genome length (kb)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α</strong></td>
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<tr>
<td>Human herpes simplex-1</td>
<td>HHV-1</td>
<td>152</td>
</tr>
<tr>
<td>Human herpes simplex-2</td>
<td>HHV-2</td>
<td>152</td>
</tr>
<tr>
<td>Varicella zoster virus (VZV)</td>
<td>HHV-3</td>
<td>125</td>
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<tr>
<td><strong>β</strong></td>
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<tr>
<td>Cytomegalovirus</td>
<td>HHV-5</td>
<td>230</td>
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<tr>
<td>Human herpesvirus-6</td>
<td>HHV-6</td>
<td>160</td>
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<tr>
<td>Human herpesvirus-7</td>
<td>HHV-7</td>
<td>145</td>
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<tr>
<td><strong>γ</strong></td>
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<tr>
<td>Epstein-Barr virus</td>
<td>HHV-4</td>
<td>172</td>
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<tr>
<td>Kaposi’s sarcoma-associated herpesvirus</td>
<td>HHV-8</td>
<td>165</td>
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</table>
Antiviral Options for the treatment of herpes viruses

- PO/IV acyclovir
- famciclovir
- valacyclovir
- IV ganciclovir
- PO valganciclovir
- IV foscarnet
- IV cidofovir
- Combination therapy

- CMV IgG
  - Leflunomide
  - Infusion of CMV-specific T-cells
Possible candidates for antiviral therapy

- Ascertain patient has ME/CFS
- PCR positive patients (EBV, HHV-6, CMV, HHV-8)
- Oral herpes (HSV-1)
- Genital herpes (HSV-2)
- Shingles (VZV)
- High titers against EBV VCA, EBV EA, HHV-6, HSV-1, HSV-2
- HHV-7, HHV-8
- Ongoing/fluctuating viral syndrome
Dose of the antiviral regimen
Change in Physical Activity and Cognitive Performance in 16 Patients Treated with Valganciclovir

Initial worsening!
Is duration of treatment important?

Response to Valganciclovir in Chronic Fatigue Syndrome Patients With Human Herpesvirus 6 and Epstein–Barr Virus IgG Antibody Titers

Tessa Watt,1 Stephanie Oberfoell,1 Raymond Balise,2 Mitchell R. Lunn,3 Aroop K. Kar,1 Lindsey Merrihew,1 Munveer S. Bhangoo,1 and José G. Montoya1,2,4,*

1Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University Medical Center, Palo Alto, California
2Stanford University School of Medicine, Health Research and Policy, Stanford, California
3Stanford University School of Medicine, Stanford, California
4Palo Alto Medical Foundation, Research Institute, Palo Alto, California
Longer valganciclovir treatment correlated with an improved response
We performed and published a randomized placebo-controlled double-blind clinical trial demonstrating the benefits of antiviral/immunomodulatory therapy.
Results in this study support the view that CFS is a real disease that necessitates sound translational research and that can be amenable to medical interventions.
Antiviral therapy of two patients with chromosomally-integrated human herpesvirus-6A presenting with cognitive dysfunction

José G. Montoya, Michael N. Neely, Sudhir Gupta, Mitchell R. Lunn, Kristin S. Loomis, Joshua C. Pritchett, Bruce Polsky, Peter G. Medveczky

Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University Medical Center, Stanford, CA 94305, USA
Department of Pediatrics, Division of Infectious Diseases, University of Southern California, Los Angeles, CA, USA
Division of Basic & Clinical Immunology, University of California, Irvine, CA, USA
Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
HHV-6 Foundation, Santa Barbara, CA, USA
Division of Infectious Disease, Department of Medicine, St. Luke's Roosevelt Hospital Center and Columbia University College of Physicians and Surgeons, New York, NY, USA
Department of Molecular Medicine, College of Medicine, University of South Florida, Tampa, FL, USA
Patient A: Absolute Power: Z Score of Delta Waves Before and After 6 Weeks of Foscarnet Therapy

Change in standard deviation from gender and age-matched controls

Before Treatment  After Treatment

Abnormal
Medical mysteries of our time that can be solved with thoughtful basic and translational research

- Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME)
- Fibromyalgia (FM)
- Gulf War illness (GWI)
- Chronic Lyme disease (CLD)
- Multiple sclerosis (MS)
“Chronic Fatigue Syndrome (CFS) or Myalgic Encephalomyelitis (ME)”

Jose G. Montoya, MD, FACP, FIDSA, Professor of Medicine, Stanford University
Director, Palo Alto Medical Foundation Toxoplasma Serology Laboratory
Palo Alto, CA
If, as human race, we were able to accomplish this

As a scientific/medical community we can solve puzzle behind CFS/ME, FM, GWI, CLD, MS and other inflammatory illnesses
MFI-20 Reduced Motivation ROIs*

Abnormal delta sources correlated with:

- **Inferior Frontal Gyrus** (BAs 9, 11, 13, 44, 45, 46, 47)
- **Medial Frontal Gyrus** (BA 32)
- **Superior/Middle Frontal Gyrus** (BAs 9, 10, 11, 46, 47)
- **Precentral Gyrus** (BAs 4, 6, 43, 44)
- **Orbital Frontal Gyrus** (BAs 11, 47)
- **Anterior Cingulate** (BA 32)
- **Insula** (BAs 13, 45)
- **Superior/Middle Temporal Gyrus** (BAs 21, 22, 38)

* All ROIs and BAs were in the left hemisphere only.
Progressive increase of inflammatory cytokines with disease severity and decrease of a key anti-inflammatory cytokine with disease duration

The perfect storm
TGF-β is a powerful anti-inflammatory cytokine.

- Promotes the development of inducible regulatory T cells (Treg cells).
- Suppresses inflammatory T-cell responses and cell-mediated immunity.
- Inhibits growth of B cells and T cells.
- Inhibits activation of macrophages.
Using LASSO, TGF-β was related to duration of illness

- Duration of Illness [continuous]
  
<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Beta coefficient</th>
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<tr>
<td>TGF-β</td>
<td>-5.2</td>
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  An one unit of decrease in log TGFB corresponds to a 5 year longer fatigue duration.

- Duration of Illness [<5 (26.0%), >=5 years (74.0%)]
  
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<th>Beta coefficient</th>
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  Patients are more likely to have the illness for longer duration with lower log TGFB.
Unfortunately she/he has had a recent and major relapse

- an inflammatory polyradiculopathy (Guillain Barre Landru syndrome), with autonomic (sympathetic and parasympathetic) involvement.

- by re-instituting antiviral and introducing anti-inflammatory treatment he appears to be improving and we hope the he has the opportunity to have a beautiful life and career again
Criteria Needed for a Fibromyalgia Diagnosis
American College of Rheumatology

1. Pain and symptoms over the past week, based on the total of:
   Number of painful areas out of 18 parts of the body
   plus
   Level of severity of these symptoms:
   Fatigue
   Waking unrefreshed
   Cognitive (memory or thought) problems
   plus
   Number of other general physical symptoms

2. Symptoms lasting at least three months at a similar level

3. No other health problem that would explain the pain and other symptoms
When to think your patient may have CFS/ME?

◆ Patient has severe and unexplained fatigue for 6 or more consecutive months that is not due to ongoing exertion

◆ Patient also complains of a spectrum of symptoms in various combinations and severity including:
  • post-exertion “crashes”, cognitive difficulties, new headaches, trouble sleeping
  • a sore throat that is frequent or recurring
  • tender cervical or axillary lymph nodes
  • muscle pain
  • multi-joint pain without swelling or redness
  • hypersensitivity to -noise, -light, or -certain food items
  • autonomic disturbances [e.g. postural orthostatic tachycardia syndrome (POTS), palpitations]
  • IBS like symptoms
  • loss of thermostat ability (e.g. intolerance of extremes of heat and cold).
We also suggest to assess severity of ME/CFS by the administration of the MFI-20* and FSS** questionnaires (7)

- **Multidimensional fatigue inventory (MFI-20) score** assesses general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. For CFS/MS patients we propose the following categories: mild (51-75), moderate (76-85) and severe (86-100)

- **Fatigue severity scale (FSS)**

- **Higher scores in the MFI-20 and/or FSS indicate increased severity**

- **Scores appear to track improvement (lower scores) or worsening (higher scores) over time**