Biomedisinske (immunologiske) studier på myalgisk encefalomyelitt (ME) / Chronic fatigue syndrome (CFS)

samlet av Eva Stormorken, 22. mars 2013

Lorusso, L., Mikhaylova, S. V., Capelli, E., Ferrari, D., Ngonga, G. K.. Ricevuti, G. Immunological aspects of chronic fatigue syndrome. *Autoimmunity Reviews,* 2009;8(4): 287-91. Link: http://www.ncbi.nlm.nih.gov/pubmed/18801465

Abstract: Chronic fatigue syndrome (CFS) is a specific clinical condition that characterises unexplained disabling fatigue and a combination of non-specific accompanying symptoms for at least 6 months, in the absence of a medical diagnosis that would otherwise explain the clinical presentation. Other common symptoms include headaches, myalgia, arthralgia, and post-exertional malaise; cognitive difficulties, with impaired memory and concentration; unrefreshing sleep; and mood changes. Similar disorders have been described for at least two centuries and have been differently named neurasthenia, post-viral fatigue, myalgic encephalomyelitis and chronic mononucleosis. Recent longitudinal studies suggest that some people affected by chronic fatigue syndrome improve with time but that most remain functionally impaired for several years. The estimated worldwide prevalence of CFS is 0.4-1% and it affects over 800,000 people in the United States and approximately 240,000 patients in the UK. No physical examination signs are specific to CFS and no diagnostic tests identify this syndrome. The pathophysiological mechanism of CFS is unclear. The main hypotheses include altered central nervous system functioning resulting from an abnormal immune response against a common antigen; a neuroendocrine disturbance; cognitive impairment caused by response to infection or other stimuli in sentient people. The current concept is that CFS pathogenesis is a multifactorial condition. Various studies have sought evidence for a disturbance in immunity in people with CFS. An alteration in cytokine profile, a decreased function of natural killer (NK) cells, a presence of autoantibodies and a reduced responses of T cells to mitogens and other specific antigens have been reported. The observed high level of pro-inflammatory cytokines may explain some of the manifestations such as fatigue and flu-like symptoms and influence NK activity. Abnormal activation of the T lymphocyte subsets and a decrease in antibody-dependent cell-mediated cytotoxicity have been described. An increased number of CD8+ cytotoxic T lymphocytes and CD38 and HLA-DR activation markers have been reported, and a decrease in CD11b expression associated with an increased expression of CD28+ T subsets has been observed. This review discusses the immunological aspects of CFS and offers an immunological hypothesis for the disease processes.

Klimas, Nancy G., Broderick, Gordon, Fletcher, Mary Ann. Biomarkers for Chronic Fatigue. *Brain, Behavior, and Immunity*, 2012; Epub ahead of print
Link: http://www.ncbi.nlm.nih.gov/pubmed/22732129

Abstract: Fatigue that persists for 6 months or more is termed chronic fatigue. Chronic fatigue (CF) in combination with a minimum of 4 of 8 symptoms and the absence of diseases that could explain these symptoms, constitute the case definition for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Inflammation, immune system activation, autonomic dysfunction, impaired functioning in the hypothalamic-pituitary-adrenal axis, and neuroendocrine dysregulation have all been suggested as root causes of fatigue. The identification of objective markers consistently associated with CFS/ME is an important goal in relation to diagnosis and treatment, as the current case definitions are based entirely on physical signs and symptoms. This review is focused on the recent literature related to biomarkers for fatigue associated with CFS/ME and, for comparison, those associated with other diseases. These markers are distributed across several of the body's core regulatory systems. A complex construct of symptoms emerges from alterations and/or dysfunctions in the nervous, endocrine and immune systems. We propose that new insight will depend on our ability to develop and deploy an integrative profiling of CFS/ME pathogenesis at the molecular level. Until such a molecular signature is obtained efforts to develop effective treatments will continue to be severely limited.

……
……

Klimas, N. G. & Koneru, A. O. Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions. *Current Rheumatology Reports*, 2007;9(6): 482-7. Link: http://www.ncbi.nlm.nih.gov/pubmed/18177602

Abstract: Investigations into the underlying cause of chronic fatigue syndrome have advanced the field considerably in the past year. Gene microarray data have led to a better understanding of pathogenesis. Recent research has evaluated genetic signatures, described biologic subgroups, and suggested potential targeted treatments. Acute viral infection studies found that initial infection severity was the single best predictor of persistent fatigue. Genomic studies showed that persistent cases express Epstein Barr virus-specific genes and demonstrate abnormalities of mitochondrial function. Studies of immune dysfunction extended observations of natural killer cytotoxic cell dysfunction of the cytotoxic T cell through quantitative evaluation of intracellular perforins and granzymes. Other research has focused on a subgroup of patients with reactivated viral infection. These advances should result in targeted therapies that impact immune function, hypothalamic-pituitary-adrenal axis regulation, and persistent viral reactivation.

……
…….

Klimas, N. G., Salvato, F. R., Morgan, R. Fletcher, M. A. Immunologic abnormalities in chronic fatigue syndrome. *Journal of Clinical Microbiology*, 1990;28(6):140

Link: http://www.ncbi.nlm.nih.gov/pubmed/2166084

Abstract: The chronic fatigue syndrome (CFS), formerly known as chronic Epstein-Barr virus syndrome, is a clinical state of some complexity and uncertain etiology. In order to characterize in a comprehensive manner the status of laboratory markers associated with cellular immune function in patients with this syndrome, 30 patients with clinically defined CFS were studied. All of the subjects were found to have multiple abnormalities in these markers. The most consistent immunological abnormality detected among these patients, when compared with normal controls, was low natural killer (NK) cell cytotoxicity. The number of NK cells, as defined by reactivity with monoclonal antibody NKH.1 (CD56), was elevated, but the killing of K562 tumor cells per CD56 cell was significantly diminished. Lymphoproliferative responses after stimulation with phytohemagglutinin and pokeweed mitogen were decreased in most patients when compared with those in normal controls, as was the production of gamma interferon following mitogen stimulation. Lymphocyte phenotypic marker analysis of peripheral blood lymphocytes showed that there were significant differences between patients with CFS and controls. There was an increase in the percentage of suppressor-cytotoxic T lymphocytes, CD8, and a proportionally larger increase in the number of CD8 cells expressing the class II activation marker. Most patients had an elevated number of CD2 cells which expressed the activation marker CDw26. The numbers of CD4 cells and the helper subset of CD4+CD29+ cells in patients with CFS were not different from those in controls. There was, however, a significant decrease in the suppressor inducer subset of CD4+ CD45RA+ cells. The number of B cells, CD20 and CD21, were elevated, as were the numbers of a subset of B cells which coexpressed CD20 and CD5. The patterns of immune marker abnormalities observed was compatible with a chronic viral reactivation syndrome.

……

Fletcher, MA., Rosenthal, M., Antoni, M., Ironson, G., Zeng, XR., Barnes, Z., Harvey, JM., Hurwitz, B., Levis, S., Broderick, G., Klimas, NG. Plasma neuropeptide Y: a biomarker for symptom severity in chronic fatigue syndrome. *Behavioral and Brain Functions*, 2010;6:76. doi:10.1186/1744-9081-6-76 Link: http://www.behavioralandbrainfunctions.com/content/6/1/76/abstract

Abstract: Background: Chronic fatigue syndrome (CFS) is a complex, multi-symptom illness with a multisystem pathogenesis involving alterations in the nervous, endocrine and immune systems. Abnormalities in stress responses have been identified as potential triggers or mediators of CFS symptoms. This study focused on the stress mediator neuropeptide Y (NPY). We hypothesized that NPY would be a useful biomarker for CFS. Methods: The CFS patients (n = 93) were from the Chronic Fatigue and Related Disorders Clinic at the University of Miami and met the 1994 case definition of Fukuda and colleagues. Healthy sedentary controls (n = 100)) were

from NIH or VA funded studies. Another fatiguing, multi-symptom illness, Gulf War Illness (GWI), was also compared to CFS. We measured NPY in plasma using a radioimmunoassay (RIA). Psychometric measures, available for a subset of CFS patients included: Perceived Stress Scale, Profile of Mood States, ATQ Positive & Negative Self-Talk Scores, the COPE, the Beck Depression Inventory, Fatigue Symptom Inventory, Cognitive Capacity Screening Examination, Medical Outcomes Survey Short Form-36, and the Quality of Life Scale. Results: Plasma NPY was elevated in CFS subjects, compared to controls (p = .000) and to GWI cases (p = . 000). Receiver operating characteristics (ROC) curve analyses indicated that the predictive ability of plasma NPY to distinguish CFS patients from healthy controls and from GWI was significantly better than chance alone. In 42 patients with CFS, plasma NPY had significant correlations (<0.05) with perceived stress, depression, anger/ hostility, confusion, negative thoughts, positive thoughts, general health, and cognitive status. In each case the correlation (+ or -) was in the anticipated direction. Conclusions: This study is the first in the CFS literature to report that plasma NPY is elevated compared to healthy controls and to a fatigued comparison group, GWI patients. The significant correlations of NPY with stress, negative mood, general health, depression and cognitive function strongly suggest that this peptide be considered as a biomarker to distinguish subsets of CFS.

……

Fletcher, M. A., Zeng, X. R., Barnes, Z., Levis, S., Klimas, N. G. Plasma cytokines in women with chronic fatigue syndrome. *Journal of Translational Medicine*, 2009;7:96. doi: 10.1186/1479-5876-7-96.Link: http://www.ncbi.nlm.nih.gov/pubmed/19909538

Abstract: BACKGROUND: Chronic Fatigue Syndrome (CFS) studies from our laboratory and others have described cytokine abnormalities. Other studies reported no difference between CFS and controls. However, methodologies varied widely and few studies measured more than 4 or 5 cytokines. Multiplex technology permits the determination of cytokines for a large panel of cytokines simultaneously with high sensitivity and with only 30 ul of plasma per sample. No widely accepted laboratory test or marker is available for the diagnosis or prognosis of CFS. This study screened plasma factors to identify circulating biomarkers associated with CFS. METHODS: Cytokines were measured in plasma from female CFS cases and female healthy controls. Multiplex technology provided profiles of 16 plasma factors including the pro -inflammatory cytokines: tumor necrosis factor alpha (TNFalpha), lymphotoxin alpha (LTalpha), interleukin (IL) - IL-Ialpha, IL-1beta, IL-6; TH1 cytokines: interferon gamma (IFNgamma), IL-12p70, IL-2, IL-15; TH2: IL-4, IL-5; TH17 cytokines, IL-17 and IL-23; anti-inflammatory cytokines IL-10, IL-13; the inflammatory mediator and neutrophil attracting chemokine IL-8 (CXCL8). Analysis by receiver operating characteristic (ROC) curve assessed the biomarker potential of each cytokine. RESULTS: The following cytokines were elevated in CFS compared to controls: LTalpha, IL-1alpha, IL-1beta, IL-4, IL-5, IL-6 and IL-12. The following cytokines were decreased in CFS:

IL-8, IL-13 and IL-15. The following cytokines were not different: TNFalpha, IFNgamma, IL-2, IL-10, IL-23 and IL-17. Applying (ROC) curve analyses, areas under the curves (AUC) for IL-5 (0. 84), LTalpha (0.77), IL-4 (0.77), IL-12 (0.76) indicated good biomarker potential. The AUC of IL-6 (0.73), IL-15 (0.73), IL-8 (0.69), IL-13 (0.68) IL-1alpha (0.62), IL-1beta (0.62) showed fair potential as biomarkers. CONCLUSION: Cytokine abnormalities are common in CFS. In this study, 10 of 16 cytokines examined showed good to fair promise as biomarkers. However, the cytokine changes observed are likely to more indicative of immune activation and inflammation, rather than specific for CFS. As such, they are targets for herapeutic strategies. Newer techniques allow evaluation of large panels of cytokines in a cost effective fashion.

……..

Fletcher, M. A., Zeng, X. R., Maher, K., Levis, S., Hurwitz, B., Antoni, M., Broderick, G., Klimas, N. G. Biomarkers in chronic fatigue syndrome: evaluation of natural killer cell function and dipeptidyl peptidase IV/CD26. *Plos One*, 2010;5:5. doi: 10.1371/journal.pone.0010817. Link: http://www.ncbi.nlm.nih.gov/pubmed/20520837

Abstract: BACKGROUND: Chronic Fatigue Syndrome (CFS) studies from our laboratory and others described decreased natural killer cell cytotoxicity (NKCC) and elevated proportion of lymphocytes expressing the activation marker, dipeptidyl peptidase IV (DPPIV) also known as CD26. However, neither these assays nor other laboratory tests are widely accepted for the diagnosis or prognosis of CFS. This study sought to determine if NKCC or DPPIV/CD26 have diagnostic accuracy for CFS. METHODS/RESULTS: Subjects included female and male CFS cases and healthy controls. NK cell function was measured with a bioassay, using K562 cells and (51)Cr release. Lymphocyte associated DPPIV/CD26 was assayed by qualitative and quantitative flow cytometry. Serum DPPIV/CD26 was measured by ELISA. Analysis by receiver operating characteristic (ROC) curve assessed biomarker potential. Cytotoxic function of NK cells for 176 CFS subjects was significantly lower than in the 230 controls. According to ROC analysis, NKCC was a good predictor of CFS status. There was no significant difference in NK cell counts between cases and controls. Percent CD2+ lymphocytes (T cells and NK cells) positive for DPPIV/C26 was elevated in CFS cases, but there was a decrease in the number of molecules (rMol) of DPPIV/C26 expressed on T cells and NK cells and a decrease in the soluble form of the enzyme in serum. Analyses by ROC curves indicated that all three measurements of DPPIV/CD26 demonstrated potential as biomarkers for CFS. None of the DPPIV/C26 assays were significantly correlated with NKCC. CONCLUSIONS: By ROC analysis, NKCC and three methods of measuring DPPIV/C26 examined in this study had potential as biomarkers for CFS. Of these, NKCC, %CD2+CD26+ lymphocytes and rMol CD26/CD2+ lymphocyte, required flow cytometry, fresh blood and access to a high complexity laboratory. Soluble DPPIV/C26 in serum is done with a standard ELISA assay, or with other soluble factors in a multiplex type of

ELISA. Dipeptidyl peptidase IV on lymphocytes or in serum was not predictive of NKCC suggesting that these should be considered as non-redundant biomarkers. Abnormalities in DPPIV/CD26 and in NK cell function have particular relevance to the possible role of infection in the initiation and/or the persistence of CFS.

Fluge, Øystein, Bruland, Ove, Risa, Kristin Storstein, Anette Kristoffersen, Einar K. Sapkota, Dipak, Næss, Halvor, Dahl, Olav, Nyland, Harald, Mella, Olav. Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study. *Plos One*, 2011;6:10. Doi: 10.1371/journal.pone.0026358 Link: http://www.ncbi.nlm.nih.gov/pubmed/22039471

Abstract: Background: Chronic fatigue syndrome (CFS) is a disease of unknown aetiology. Major CFS symptom relief during cancer chemotherapy in a patient with synchronous CFS and lymphoma spurred a pilot study of B-lymphocyte depletion using the anti-CD20 antibody Rituximab, which demonstrated significant clinical response in three CFS patients. Methods and findings: In this double-blind, placebo-controlled phase II study (NCT00848692), 30 CFS patients were randomised to either Rituximab 500 mg/m(2) or saline, given twice two weeks apart, with follow-up for 12 months. Xenotropic murine leukemia virus-related virus (XMRV) was not detected in any of the patients. The responses generally affected all CFS symptoms. Major or moderate overall response, defined as lasting improvements in self-reported Fatigue score during follow-up, was seen in 10 out of 15 patients (67%) in the Rituximab group and in two out of 15 patients (13%) in the Placebo group (p=0.003). Mean response duration within the follow-up period for the 10 responders to Rituximab was 25 weeks (range 8-44). Four Rituximab patients had clinical response durations past the study period. General linear models for repeated measures of Fatigue scores during follow-up showed a significant interaction between time and intervention group (p=0.018 for self-reported, and p=0.024 for physician-assessed), with differences between the Rituximab and Placebo groups between 6-10 months after intervention. The primary end-point, defined as effect on self-reported Fatigue score 3 months after intervention, was negative. There were no serious adverse events. Two patients in the Rituximab group with pre-existing psoriasis experienced moderate psoriasis worsening. Conclusion: The delayed responses starting from 2-7 months after Rituximab treatment, in spite of rapid B-cell depletion, suggests that CFS is an autoimmune disease and may be consistent with the gradual elimination of autoantibodies preceding clinical responses. The present findings will impact future research efforts in CFS. Trial registration: ClinicalTrials.gov NCT00848692.

……

Fluge, O. & Mella, O. Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: a preliminary case series. *BMC Neurology*, 2009;9:28.doi: 10.1186/1471-2377-9-28. Link: http://www.ncbi.nlm.nih.gov/pubmed/19566965

Abstract: BACKGROUND: Chronic fatigue syndrome (CFS) is a disease of unknown aetiology. A patient with CFS had unexpected, marked recovery of CFS symptoms lasting for five months during and after cytotoxic chemotherapy for Hodgkin's disease. We reasoned that the transient CFS recovery was related to methotrexate treatment, which induces immunomodulation in part through B-cell depletion.

METHODS: In a case series, this patient and two additional CFS patients were B-cell depleted by infusion of the monoclonal anti-CD20 antibody rituximab. RESULTS: All three had improvement of all CFS symptoms. Patients 1 and 2 had major amelioration from 6 weeks after intervention, patient 3 slight improvement from the same time, but then improved markedly from 26 weeks after intervention. The symptomatic effect lasted until weeks 16, 18 and 44, respectively. At relapse, all were retreated with a single (patient 1) or double rituximab infusion (patients 2 and 3). Again, all three had marked symptom improvement, mimicking their first response. After new symptom recurrence, patients 1 and 2 were given weekly oral methotrexate, patient 1 having effect also from this agent. Patients 1 and 2 were again treated for a third rituximab infusion after new relapse, again with a marked clinical benefit. No unexpected toxicity was seen. CONCLUSION: These observations suggest that B-lymphocytes are involved in CFS pathogenesis for a subset of patients. Benefit for all CFS symptoms, the delayed symptom relief following B-cell depletion, the kinetics of relapses, and the effect also from methotrexate treatment, provide suggestive evidence that B-cells play a significant role in the ongoing clinical features, and that CFS may be amenable to therapeutic interventions aimed at modifying B-cell number and function. More systematic investigations of this therapeutic strategy, and of its biological basis, are now needed.

……..

Levine, P. H., Peterson, D., McNamee, F. L., O'Brien, K., Gridley, G., Hagerty, M., Brady, J., Fears, T., Atherton, M., Hoover, R. Does chronic fatigue syndrome predispose to non-Hodgkin's lymphoma? *Cancer Research*, 1992;52(19 suppl): 5516s-5518s; discussion 5518s-5521s. Link: http://www.ncbi.nlm.nih.gov/pubmed/1394166

Abstract: Chronic fatigue syndrome, an illness that frequently is associated with abnormalities of cellular immunity, has been reported anecdotally to be associated with an increased incidence of lymphoid hyperplasia and malignancy. This report describes an initial analysis of population-based cancer incidence data in Nevada, focusing on the patterns of non-Hodgkin's lymphoma prior to and subsequent to well described, documented outbreaks of chronic fatigue syndrome during 1984-1986. In a study of time trends in four age groups, the observed time trends were consistent with the national trends reported in the Surveillance, Epidemiology, and End Results Program. No statistically significant increase attributable to the chronic fatigue syndrome outbreak was identified at the state level. Additional studies are in progress analyzing the data at the country level, reviewing patterns in other malignancies, and continuing to monitor the cancer patterns over subsequent years.

……

Chang, Cindy M., Warren, Joan L., Engels, Eric A. Chronic fatigue syndrome and subsequent risk of cancer among elderly US adults. *Cancer*, 2012; Epub ahead of print. doi: 10.1002/cncr.27612. Link: http://www.ncbi.nlm.nih.gov/pubmed/22648858

Abstrakt: BACKGROUND: The cause of chronic fatigue syndrome (CFS) is unknown but is thought to be associated with immune abnormalities or infection. Because cancer can arise from similar conditions, associations between CFS and cancer were examined in a population-based case-control study among the US elderly. METHODS: Using linked Surveillance, Epidemiology, and End Results (SEER)-Medicare registry data, approximately 1.2 million cancer cases and 100,000 controls (age range, 66-99 years; 1992-2005) were evaluated. CFS was identified in the period more than 1 year prior to selection, using linked Medicare claims. Unconditional logistic regression was used to estimate the odds ratios (ORs) comparing the CFS prevalence in cases and controls, adjusting for age, sex, and selection year. All statistical tests were 2-sided. RESULTS: CFS was present in 0.5% of cancer cases overall and 0.5% of controls. CFS was associated with an increased risk of non-Hodgkin lymphoma (NHL**)** (OR = 1.29, 95% confidence interval [CI] = 1.16-1.43, P = 1.7 × 10−6). Among NHL subtypes, CFS was associated with diffuse large B cell lymphoma (OR = 1.34, 95% CI = 1.12-1.61), marginal zone lymphoma (OR = 1.88, 95% CI = 1.38-2.57), and B cell NHL not otherwise specified (OR = 1.51, 95% CI = 1.03-2.23). CFS associations with NHL overall and NHL subtypes remained elevated after excluding patients with medical conditions related to CFS or NHL, such as autoimmune conditions. CFS was also associated, although not after multiple comparison adjustment, with cancers of the pancreas (OR = 1.25, 95% CI = 1.07-1.47), kidney (OR = 1.27, 95% CI = 1.07-1.49), breast (OR = 0.85, 95% CI = 0.74-0.98), and oral cavity and pharynx (OR = 0.70, 95% CI = 0.49-1.00). CONCLUSIONS: Chronic immune activation or an infection associated with CFS may play a role in explaining the increased risk of NHL.

……

Levine, P. H., Fears, T. R., Cummings, P., Hoover, R. N. Cancer and a fatiguing illness in Northern Nevada--a causal hypothesis. *Annals of Epidemiology*, 1998;8(4): 245-9. Link: http://www.ncbi.nlm.nih.gov/pubmed/9590603

Abstract: PURPOSE: We investigated the possibility that chronic fatigue syndrome (CFS) predisposes to cancer by comparing the cancer pattern in an area in northern Nevada, where an outbreak of a fatiguing illness, which included cases of CFS, was reported, to an area in southern Nevada, where no such illness was reported. METHODS: Data from the computerized Nevada Cancer Registry were utilized to compare incidence rates of four malignancies--brain cancer, non-Hodgkin lymphoma (NHL), lung cancer, and breast cancer--in Washoe and Lyon Counties, where an unexplained fatiguing illness was reported during 1984-86, with comparably sized Clark County, where no such illness was reported. RESULTS: Higher incidences of NHL and primary brain tumors were noted in the two northern Nevada counties (Washoe and Lyon) in 1986 and 1987 respectively, compared to the southern Nevada (Clark) county. Similar patterns were not seen for breast or lung cancer. CONCLUSIONS: This study provides a model for investigating the possible predisposition of CFS patients to develop cancer using other cohorts, but it is currently premature to accept such a link at this time.

Levine, P. H., Atherton, M., Fears, T., Hoover, R. An approach to studies of cancer subsequent to clusters of chronic fatigue syndrome: use of data from the Nevada State Cancer Registry. *Clinical Infectious Diseases*, 1994;18(Suppl 1): S49-53.

Abstract: Chronic fatigue syndrome (CFS) has been increasingly associated with immune dysregulation, including depressed natural killer cell activity; this phenomenon is associated with increased susceptibility to cancer. Although anecdotal reports have suggested an association between CFS and cancer, particularly non-Hodgkin's lymphoma and brain cancer, there has been no a priori justification for evaluating such an association and no consideration of relevant parameters, such as length of latent period vs. tumor type. We reviewed data from the Nevada State Cancer Registry subsequent to a reported outbreak of a CFS-like illness in Nevada that occurred during 1984-1986. We concentrated on non-Hodgkin's lymphoma and brain/CNS tumors, with particular emphasis on persons 15-34 and 35-54 years of age. An upward trend in the incidence of brain/CNS tumors, which could be related to a national upward trend for this disease, was noted. No consistent trends were noted for non-Hodgkin's lymphoma. Because of the difficulties inherent in studies of cancer subsequent to various exposures, we evaluated the methodology for determining an association between outbreaks of CFS-like disease and cancer. We propose several approaches that should be considered in future studies for investigation of possible associations between CFS and cancer, including expected latent periods for specific tumors.

……

Levine, P. H., Atherton, M., Fears, T., Hoover, R. An approach to studies of cancer subsequent to clusters of chronic fatigue syndrome: use of data from the Nevada State Cancer Registry. *Clinical Infectious Diseases*, 18(Suppl 1): S49-53. Link: http://www.ncbi.nlm.nih.gov/pubmed/8148453

Abstract: Chronic fatigue syndrome (CFS) has been increasingly associated with immune dysregulation, including depressed natural killer cell activity; this phenomenon is associated with increased susceptibility to cancer. Although anecdotal reports have suggested an association between CFS and cancer, particularly non-Hodgkin's lymphoma and brain cancer, there has been no a priori justification for evaluating such an association and no consideration of relevant parameters, such as length of latent period vs. tumor type. We reviewed data from the Nevada State Cancer Registry subsequent to a reported outbreak of a CFS-like illness in Nevada that occurred during 1984-1986. We concentrated on non-Hodgkin's lymphoma and brain/CNS tumors, with particular emphasis on persons 15-34 and 35-54 years of age. An upward trend in the incidence of brain/CNS tumors, which could be related to a national upward trend for this disease, was noted. No consistent trends were noted for non-Hodgkin's lymphoma. Because of the difficulties inherent in studies of cancer subsequent to various exposures, we evaluated the methodology for determining an association between outbreaks of CFS-like disease and cancer. We propose several approaches that should be

considered in future studies for investigation of possible associations between CFS and cancer, including expected latent periods for specific tumors.

Siegel, S. D., Antoni, M. H., Fletcher, M. A., Maher, K., Segota, M. C., Klimas, N. Impaired natural immunity, cognitive dysfunction, and physical symptoms in patients with chronic fatigue syndrome: preliminary evidence for a subgroup? *Journal of Psychosomatic Research*, 2006;60(6): 559-66. Link: http://www.ncbi.nlm.nih.gov/pubmed/16731230

Abstract: OBJECTIVE: The diagnostic criteria of chronic fatigue syndrome (CFS) define a heterogeneous population composed of several subgroups. Past efforts to identify subgroup markers have met with mixed success. This study was designed to examine natural killer cell activity (NKCA) as a potential subgroup marker by comparing the clinical presentations of CFS patients with and without clinically reduced NKCA. METHODS: Forty-one female CFS patients were classified into having either low or normal NKCA levels. These subgroups were then compared on objective measures of cognitive functioning and subjective assessments of fatigue, vigor, cognitive impairment, and daytime dysfunction. RESULTS: Relative to CFS patients in the normal-NKCA subgroup, low-NKCA patients reported less vigor, more daytime dysfunction, and more cognitive impairment. In addition, low-NKCA patients performed less on objective measures of cognitive functioning relative to normal-NKCA patients. CONCLUSIONS: The results are offered as preliminary evidence in support of using NKCA as an immunological subgroup marker in CFS. Findings are also discussed in terms of known associations between dysregulated immune functions, somatic symptoms, and psychological stress.

……..

Meeus, M., Mistiaen, W., Lambrecht, L., Nijs, J. Immunological similarities between cancer and chronic fatigue syndrome: the common link to fatigue? *Anticancer Research*, 2009;29(11): 4717-26. Link: http://www.ncbi.nlm.nih.gov/pubmed/20032425

Abstract: Cancer and chronic fatigue syndrome (CFS) are both characterised by fatigue and severe disability. Besides fatigue, certain aspects of immune dysfunctions appear to be present in both illnesses. In this regard, a literature review of overlapping immune dysfunctions in CFS and cancer is provided. Special emphasis is given to the relationship between immune dysfunctions and fatigue. Abnormalities in ribonuclease (RNase) L and hyperactivation of nuclear factor kappa beta (NF-kappaB) are present in CFS and in prostate cancer. Malfunctioning of natural killer (NK) cells has long been recognised as an important factor in the development and reoccurrence of cancer, and has been documented repeatedly in CFS patients. The dysregulation of the RNase L pathway, hyperactive NF-kappaB leading to disturbed apoptotic mechanisms and oxidative stress or excessive nitric oxide, and low NK activity may play a role in the two diseases and in the physiopathology of the common symptom fatigue. However, in cancer the relation between the immune dysfunctions and fatigue has been poorly studied. Immunological abnormalities to such as a dysregulated RNase L pathway, hyperactive NF-kappaB, increased

oxidative stress and reduced NK cytotoxicity, among others, are present in both diseases. These anomalies may be part of the physiopathology of some of the common complaints, such as fatigue. Further studies to confirm the hypotheses given here are warranted.

Jason, L. A., Corradi, K., Gress, S., Williams, S., Torres-Harding, S. Causes of death among patients with chronic fatigue syndrome. *Health Care for Women International*, 2006;27(7): 615-26. Link: http://www.ncbi.nlm.nih.gov/pubmed/16844674

Abstract: Chronic fatigue syndrome (CFS) is a debilitating illness affecting thousands of individuals. At the present time, there are few studies that have investigated causes of death for those with this syndrome. The authors analyzed a memorial list tabulated by the National CFIDS Foundation of 166 deceased individuals who had had CFS. There were approximately three times more women than men on the list. The three most prevalent causes of death were heart failure, suicide, and cancer, which accounted for 59.6% of all deaths. The mean age of those who died from cancer and suicide was 47.8 and 39.3 years, respectively, which is considerably younger than those who died from cancer and suicide in the general population. The implications of these findings are discussed.

……

Maes, M. & Twisk, F. N. Why myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may kill you: disorders in the inflammatory and oxidative and nitrosative stress (IO&NS) pathways may explain cardiovascular disorders in ME/CFS. *Neuroendocrinology Letters*, 2009;30(6): 677-93. Link: http://www.ncbi.nlm.nih.gov/pubmed/20038921

Abstract: There is evidence that disorders in inflammatory and oxidative and nitrosative (IO&NS) pathways and a lowered antioxidant status are important pathophysiological mechanisms underpinning myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS). Important precipitating and perpetuating factors for ME/CFS are (amongst others) bacterial and viral infections; bacterial translocation due to an increased gut permeability; and psychological stress. Recently, Jason et al (2006) reported that the mean age of patients with myalgic encephalomyelitis/chronic fatigue syndrome dying from heart failure, i.e. 58.7 years, is significantly lower than the age of those dying from heart failure in the general US population, i.e. 83.1 years. These findings implicate that ME/CFS is a risk factor to cardio-vascular disorder. This review demonstrates that disorders in various IO&NS pathways provide explanations for the earlier mortality due to cardiovascular disorders in ME/CFS. These pathways are: a) chronic low grade inflammation with extended production of nuclear factor kappa B and COX-2 and increased levels of tumour necrosis factor alpha; b) increased O&NS with increased peroxide levels, and phospholipid oxidation including oxidative damage to phosphatidylinositol; c) decreased levels of specific antioxidants, i.e. coenzyme Q10, zinc and dehydroepiandrosterone-sulphate; d) bacterial translocation as a result of leaky gut; e) decreased omega-3 polyunsatutared fatty acids (PUFAs), and increased omega-6 PUFA and saturated fatty acid levels; and f) the presence of viral and bacterial infections and psychological stressors. The mechanisms whereby each of these factors may contribute towards cardio-vascular disorder in ME/CFS are discussed. ME/CFS is a multisystemic metabolic-inflammatory disorder. The aberrations in IO&NS pathways may increase the risk for cardiovascular disorders.

Chao, C. C., Janoff, E. N., Hu, S. X., Thomas, K., Gallagher, M., Tsang, M., Peterson, P. K. Altered cytokine release in peripheral blood mononuclear cell cultures from patients with the chronic fatigue syndrome. *Cytokine*, 1991;3(4): 292-8. Link: http://www.ncbi.nlm.nih.gov/pubmed/1873478

Abstract: Chronic fatigue syndrome (CFS) is an idiopathic illness associated with a variety of immunologic abnormalities. To investigate potential pathogenetic mechanisms, we evaluated serum levels and peripheral blood mononuclear cell (PBMC) production of selected cytokines and immunoglobulins. Serum bioactive transforming growth factor beta (TGF-beta) levels were higher (P less than 0.01) in patients with CFS (290 +/- 46 pg/mL) than in control subjects (104 +/- 18 pg/mL), but levels of other cytokines tested were not different. Lipopolysaccharide-stimulated release of interleukin 1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha was increased (P less than 0.05) in PBMC cultures from patients with CFS versus control subjects; enhanced (P less than 0.01) IL-6 release to phytohemagglutinin was also observed. In contrast, TGF-beta release in response to lipopolysaccharide was depressed (P less than 0.01) in PBMC cultures derived from patients with CFS. No differences in IL-2 and IL-4 or immunoglobulin production were observed. The enhanced release of inflammatory cytokines by stimulated PBMC from patients with CFS suggests that these cells are primed for an increased response to immune stimuli. These data also suggest an association between abnormal regulation of TGF-beta production in vivo and in vitro with the immunologic consequence of CFS.

……..

Kerr, JR & Cunniffe, VS. Antibodies to parvovirus B19 non-structural protein are associated with chronic but not acute arthritis following B19 infection. *Rheumatology*, 2000;39(8): 903-908. Link: http://www.ncbi.nlm.nih.gov/pubmed/10952747

Abstract: Objective. To determine the incidence and significance of antibodies to the parvovirus B19 non-structural (NS1) protein in B19-infected persons during acute infection and convalescence.|Methods. The B19 NS1 protein was expressed in SF9 cells using the baculovirus expression system and was used to prepare immunofluorescence slides. These were used in a fluorescent antibody test to determine anti-B19 NS1 IgG in a well-characterized cohort of 53 persons at the time of acute B19 infection and again after a follow-up period of 26-85 months. Results were examined for statistical significance by the use of Fisher's exact test.|Results. NS1 antibodies were detected in five of 32 persons with acute B19 infection (four with arthritis) and 10 of 53 persons with past B19 infection (six with chronic arthritis and two with chronic arthritis and chronic fatigue syndrome). Regarding the correlation of NS1 antibodies and arthritis, at the time of acute infection four of 24 per sons with arthritis had NS1 antibodies detected compared with one of eight persons with any other symptoms (P = 1). During convalescence, eight of 20 persons with chronic arthritis had NS1 antibodies compared with two of 33 with symptoms of any other category tall except one were asymptomatic) (P = 0.007). All 10 patients with NS1 antibodies during convalescence had arthritis during acute infection. which persisted in eight persons until the time of follow-up.|Conclusion. Antibodies to

parvovirus B19 NS1 protein are associated with chronic but not with acute arthritis after B19 infection.

Kerr, J. R. Gene profiling of patients with chronic fatigue syndrome/myalgic encephalomyelitis. *Current Rheumatology Reports*, 2008;10(6): 482-91. Link: http://www.ncbi.nlm.nih.gov/pubmed/19007540

Abstract: Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a multisystem disease, the pathogenesis of which remains undetermined. Following two microarray studies, we reported the differential expression of 88 human genes in patients with CFS; 85 of these genes were upregulated and 3 were downregulated. The top functional categories of these 88 genes were hematologic disease and function, immunologic disease and function, cancer, cell death, immune response, and infection. Clustering of quantitative polymerase chain reaction data from CFS/ME patients revealed seven subtypes with distinct differences in Short Form (SF)-36 scores, clinical phenotypes, and severity. Gene signatures in each subtype implicate five human genes as possible targets for specific therapy. Development of a diagnostic test for subtype status is now a priority. The possibility that these subtypes represent individual host responses to particular microbial infections is being investigated and may provide another route to specific therapies for CFS patients.

……

Kerr, J. R., Burke, B., Petty, R., Gough, J., Fear, D., Mattey, D. L., Axford, J. S., Dalgleish, A. G., Nutt, D. J. Seven genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis: a detailed analysis of gene networks and clinical phenotypes. *Journal of Clinical Pathology*, 2008:61(6): 730-9.
Link: http://www.ncbi.nlm.nih.gov/pubmed/18057078

Abstract: AIM: Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a multisystem disease, the pathogenesis of which remains undetermined. The authors have recently reported a study of gene expression that identified differential expression of 88 human genes in patients with CFS/ME. Clustering of quantitative PCR (qPCR) data from patients with CFS/ME revealed seven distinct subtypes with distinct differences in Medical Outcomes Survey Short Form-36 scores, clinical phenotypes and severity. METHODS: In this study, for each CFS/ME subtype, those genes whose expression differed significantly from that of normal blood donors were identified, and then gene interactions, disease associations and molecular and cellular functions of those gene sets were determined. Genomic analysis was then related to clinical data for each CFS/ME subtype. RESULTS: Genomic analysis revealed some common (neurological, haematological, cancer) and some distinct (metabolic, endocrine, cardiovascular, immunological, inflammatory) disease associations among the subtypes. Subtypes 1, 2 and 7 were the most severe, and subtype 3 was the mildest. Clinical features of each subtype were as follows: subtype 1 (cognitive, musculoskeletal, sleep, anxiety/depression); subtype 2 (musculoskeletal, pain, anxiety/depression); subtype 3 (mild); subtype 4 (cognitive); subtype 5 (musculoskeletal, gastrointestinal); subtype 6 (postexertional); subtype 7 (pain, infectious, musculoskeletal, sleep, neurological, gastrointestinal, neurocognitive, anxiety/depression). CONCLUSION: It was particularly interesting that in the seven genomically derived subtypes there were distinct clinical

syndromes, and that those which were most severe were also those with anxiety/ depression, as would be expected in a disease with a biological basis.

Brenu EW, van Driel ML, Staines DR, Ashton KJ, Hardcastle SL, Keane J, et al. Longitudinal investigation of naturl killer celles and cytokines inchronic fatigue syndrome/myalgic encephalomyelitis. *Journal of Translational Medicine*. 2012;10(1): 88. http://www.ncbi.nlm.nih.gov/pubmed/22571715 http://www.translational-medicine.com/content/pdf/1479-5876-10-88.pd f http://www.translational-medicine.com/content/10/1/88/abstract

Abstract: BACKGROUND: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is an etiologically unexplained disorder characterised by irregularities in various aspects of the immunological function. Presently, it is unknown whether these immunological changes remain consistent over time. This study investigates Natural Killer (NK) cell cytotoxic activity, NK cell subsets (CD56brightCD16- and CD56dimCD16+) and cytokines, over the course of a12 month period in patients with CFS/ME. METHODS: The participants in the study comprised 65 (47.2+/-11.5 years) CFS/ME participants and 21 (45.2 +/-9.3 years) non-fatigued controls. Flow cytometry protocols were used to assess NK subsets and NK cytotoxic activity at various time points that included baseline (T1), 6 (T2) and 12 months (T3). Cytokine secretions were measured following mitogenic stimulation of peripheral blood mononuclear cells. RESULTS: NK cytotoxic activity was significantly decreased in the CFS/ME patients at T1, T2 and T3 compared to the non-fatigued group. Additionally, in comparison to the non-fatigued controls, the CFS/ME group had significantly lower numbers of CD56brightCD16- NK cells at both T1 and T2. Interestingly, following mitogenic stimulation, cytokine secretion revealed significant increases in IL-10, IFN-gamma and TNF-alpha at T1 in the CFS/ME group. A significant decrease was observed at T2 in the CFS/ME group for IL-10 and IL-17A while at T3, IL-2 was increased in the CFS/ME group in comparison to the non- fatigued controls. Overall cytotoxic activity was significantly decreased at T3 compared to T1 and T2. CD56brightCD16- NK cells were much lower at T2 compared to the T1 and T3. IL-10 and IL-17A secretion was elevated at T2 in comparison to the T1 and T3. CONCLUSION: These results confirm decreases in immune function in CFS/ME patients, suggesting an increased susceptibility to viral and other infections. Furthermore NK cytotoxic activity may be a suitable biomarker for diagnosing CFS/ ME as it was consistently decreased during the course of the 12 months study.

……

Brenu, E. W., Staines, D. R. Baskurt, O. K., Ashton, K. J., Ramos, S. B., Christy, R. M., Marshall-Gradisnik, S. M. Immune and hemorheological changes in chronic fatigue syndrome. *Journal of Translational Medicine*. 2010;8:10. http://www.ncbi.nlm.nih.gov/pubmed/20064266 http://www.translational-medicine.com/content/pdf/1479-5876-8-1.pdf

Abstract: BACKGROUND: Chronic Fatigue Syndrome (CFS) is a multifactorial disorder that affects various physiological systems including immune and neurological systems. The immune system has been substantially examined in CFS

with equivocal results, however, little is known about the role of neutrophils and natural killer (NK) phenotypes in the pathomechanism of this disorder. Additionally the role of erythrocyte rheological characteristics in CFS has not been fully expounded. The objective of this present study was to determine deficiencies in lymphocyte function and erythrocyte rheology in CFS patients. METHODS: Flow cytometric measurements were performed for neutrophil function, lymphocyte numbers, NK phenotypes (CD56(dim)CD16(+) and CD56(bright)CD16(-)) and NK cytotoxic activity. Erythrocyte aggregation, deformability and fibrinogen levels were also assessed. RESULTS: CFS patients (n = 10) had significant decreases in neutrophil respiratory burst, NK cytotoxic activity and CD56(bright)CD16(-) NK phenotypes in comparison to healthy controls (n = 10). However, hemorheological characteristic, aggregation, deformability, fibrinogen, lymphocyte numbers and CD56(dim)CD16(+) NK cells were similar between the two groups. CONCLUSION: These results indicate immune dysfunction as potential contributors to the mechanism of CFS, as indicated by decreases in neutrophil respiratory burst, NK cell activity and NK phenotypes. Thus, immune cell function and phenotypes may be important diagnostic markers for CFS. The absence of rheological changes may indicate no abnormalities in erythrocytes of CFS patients.

……

Brenu, E. W., Ashton, K. J., van Driel, M., Staines, D. R., Peterson, D., Atkinson, G. M., Marshall-Gradisnik, S. M.
Cytotoxic lymphocyte microRNAs as prospective biomarkers for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *Journal of Affective Disorders*. 2012;141(2-3): 261-9. http://www.ncbi.nlm.nih.gov/pubmed/22572093

Abstract: BACKGROUND: Immune dysfunction associated with a disease often has a molecular basis. A novel group of molecules known as microRNAs (miRNAs) have been associated with suppression of translational processes involved in cellular development and proliferation, protein secretion, apoptosis, immune function and inflammatory processes. MicroRNAs may be implicated in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), where immune function is impaired. The objective of this study was to determine the association between miRNAs in cytotoxic cells and CFS/ME. METHODS: Natural Killer (NK) and CD8(+)T cells were preferentially isolated from peripheral blood mononuclear cells from all participants (CFS/ME, n=28; mean age=41.8+/-9.6years and controls, n=28; mean age=45.3+/-11.7years), via negative cell enrichment. Following total RNA extraction and subsequent synthesis of cDNA, reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) was used to determine the expression levels of nineteen miRNAs. RESULTS: There was a significant reduction in the expression levels of miR-21, in both the NK and CD8(+)T cells in the CFS/ME sufferers. Additionally, the expression of miR-17-5p, miR-10a, miR-103, miR-152, miR-146a, miR-106, miR-223 and miR-191 was significantly decreased in NK cells of CFS/ME patients in comparison to the non-fatigued controls. LIMITATIONS: The results from these

investigations are not yet transferable into the clinical setting, further validatory studies are now required. CONCLUSIONS: Collectively these miRNAs have been associated with apoptosis, cell cycle, development and immune function. Changes in miRNAs in cytotoxic cells may reduce the functional capacity of these cells and disrupt effective cytotoxic activity along with other immune functions in CFS/ME patients.

……

Brenu, EW., Ashton, KJ., Atkinson, Gunn M., Staines, Donald R., Marshall-Gradisnik, S. Gene Expression in Chronic Fatigue Syndrome (Chap. 2, pp. 13-46). In. *An International Perspective on the Future of Research in Chronic Fatigue Syndrome*. Rijeka, Croatia: InTech, 2012. ISBN: 978-953-51-0072-0 http://www.intechopen.com/articles/show/title/gene-expression-in-chronic-fatigue-syndrome http://www.intechopen.com/source/pdfs/28108/InTech-Gene_expression_in_chronic_fatigue_syndrome.pdf

……

Brenu, E., van Driel, M., Staines, D., Ashton, K., Ramos, S., Keane, J., Klimas, N., Marshall-Gradisnik, S. Immunological abnormalities as potential biomarkers in Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis. *Journal of Translational Medicine*. 2011;9(1):81.
http://www.translational-medicine.com/content/9/1/81
http://www.translational-medicine.com/content/pdf/1479-5876-9-81.pdf

Abstract: BACKGROUND:Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is characterized by severe prolonged fatigue, and decreases in cognition and other physiological functions, resulting in severe loss of quality of life, difficult clinical management and high costs to the health care system. To date there is no proven pathomechanism to satisfactorily explain this disorder. Studies have identified abnormalities in immune function but these data are inconsistent. We investigated the profile of markers of immune function (including novel markers) in CFS/ME patients.METHODS:We included 95 CFS/ME patients and 50 healthy controls. All participants were assessed on natural killer (NK) and CD8+T cell cytotoxic activities, Th1 and Th2 cytokine profile of CD4+T cells, expression of vasoactive intestinal peptide receptor 2 (VPACR2), levels of NK phenotypes (CD56bright and CD56dim) and regulatory T cells expressing FoxP3 transcription factor. RESULTS:Compared to healthy individuals, CFS/ME patients displayed significant increases in IL-10, IFN-gamma, TNF-alpha, CD4+CD25+ T cells, FoxP3 and VPACR2 expression. Cytotoxic activity of NK and CD8+T cells and NK phenotypes, in particular the CD56bright NK cells were significantly decreased in CFS/ME patients. Additionally granzyme A and granzyme K expression were reduced while expression levels of perforin were significantly increased in the CFS/ME population relative to the control population. These data suggest significant dysregulation of the immune system in CFS/ME patients. CONCLUSIONS:Our study found immunological abnormalities which may

serve as biomarkers in CFS/ME patients with potential for an application as a diagnostic tool.

Bradley, A.S., Ford, B., Bansal, A.S. Altered functional B cell subset populations in patients with chronic fatigue syndrome compared to healthy controls. *Clinical and Experimental Immunology*. 2013;172(1):73-80.
http://onlinelibrary.wiley.com/doi/10.1111/cei.12043/pdf
http://onlinelibrary.wiley.com/doi/10.1111/cei.12043/abstract
http://www.ncbi.nlm.nih.gov/pubmed/23480187

Abstract: Chronic fatigue syndrome (CFS) is a heterogeneous disorder of unknown aetiology characterized by disabling fatigue, headaches, sleep disturbance and several other symptoms. The onset of CFS may follow a viral infection or period of stress. Patients with CFS do not have hypogammaglobulinaemia, predisposition to recurrent bacterial infections or symptoms of autoimmunity. To date, defects in B cell numbers or function have not been shown in the literature. However, treatment with anti-B cell therapy using Rituximab has recently shown benefit to CFS patients. We therefore postulated that patients with CFS had a subtle humoral immune dysfunction, and performed extended B cell immunophenotyping. We undertook a detailed characterization of the proportions of the different B cell subsets in 33 patients with CFS fulfilling the Canadian and Fukuda criteria for CFS and compared these with 24 age- and gender-matched healthy controls (HC). CFS patients had greater numbers of naive B cells as a percentage of lymphocytes: 6.3 versus 3.9% in HC (P = 0.034), greater numbers of naive B cells as a percentage of B cells: 65 versus 47% in controls (P = 0.003), greater numbers of transitional B cells: 1.8 versus 0.8% in controls (P = 0.025) and reduced numbers of plasmablasts: 0.5 versus 0.9% in controls (P = 0.013). While the cause of these changes is unclear, we speculate whether they may suggest a subtle tendency to autoimmunity.

……

Curriu, M., Carrillo, J., Massanella, M., Rigau, J., Alegre, J., Puig, J., Garcia-Quintana, A. M., Castro-Marrero, J., Negredo, E., Clotet, B., Cabrera, C., Blanco, J. Screening NK-, B- and T-cell phenotype and function in patients suffering from Chronic Fatigue Syndrome. *Journal of Translational Medicine*. 2013;11(1):68.
http://www.translational-medicine.com/content/11/1/68/abstract
http://www.translational-medicine.com/content/pdf/1479-5876-11-68.pdf
http://www.ncbi.nlm.nih.gov/pubmed/23514202

Abstract: BACKGROUND: Chronic Fatigue Syndrome (CFS) is a debilitating neuro-immune disorder of unknown etiology diagnosed by an array of clinical manifestations. Although several immunological abnormalities have been described in CFS, their heterogeneity has limited diagnostic applicability. METHODS: Immunological features of CFS were screened in 22 CFS diagnosed individuals fulfilling Fukuda criteria and 30 control healthy individuals. Peripheral blood T, B and NK cell function and phenotype were analyzed by flow cytometry in both groups. RESULTS: CFS diagnosed individuals showed similar absolute numbers of T, B and NK cells, with minor differences in the percentage of CD4+ and CD8+ T cells. B cells showed similar subset frequencies and proliferative responses between groups.

Conversely, significant differences were observed in T cell subsets. CFS individuals showed increased levels of T regulatory cells (CD25+/FOXP3+) CD4 T cells, and lower proliferative responses in vitro and in vivo. Moreover, CD8 T cells from the CFS group showed significantly lower activation and frequency of effector memory cells. No clear signs of T-cell immunosenescence were observed. NK cells from CFS individuals displayed higher expression of NKp46 and CD69 but lower expression of CD25 in all NK subsets defined. Overall, T cell and NK cell features clearly clustered CFS individuals. CONCLUSIONS: Our findings suggest that alterations in T-cell phenotype and proliferative response along with the specific signature of NK cell phenotype may be useful to identify CFS individuals. The striking down modulation of T cell mediated immunity may help to understand intercurrent viral infections in CFS.