Mental fatigue after allogeneic hematopoietic stem cell transplantation is associated with cognitive dysfunction, but not central nervous system inflammation

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doi:10.3324/haematol.2019.225326

Supplementary material

Supplemental methods

Study design

This was a descriptive cross-sectional pilot study on patients with and without mental fatigue, 1-5 years after allogeneic hematopoietic stem cell transplantation (aHSCT) for haematological disease. The two study groups were 1) patients with self-reported symptoms of mental fatigue and a high score on the mental fatigue scale (MFS≥14 points) and 2) patients with absence of self-reported symptoms of mental fatigue and a low score on the MFS (≤10 points).

The study participants were recruited at the Department of Hematology, Karolinska University Hospital (KUS), Huddinge, Sweden. We randomly selected patients fluent in the Swedish language, aged >18 years, that underwent aHSCT 1-5 years ago and did not meet exclusion criteria 1-7 that we could assess based on the patient medical records. Patients with a medical history suggesting an alternative cause of mental fatigue were excluded. This included severe psychiatric disorders, structural or metabolic neurological disorders, as well as certain treatments affecting CNS function, such as irradiation to the brain (resulting from TBI), intrathecal chemotherapy, significant doses of sedatives, opioids or neuroleptic drugs and substance abuse. Further, patients that would be unable to participate in the study evaluations were excluded, i.e. those with magnetic implants, bleeding tendencies, signs of increased intracranial pressure or infections at the site of a lumbar puncture. Finally, patients on ≥ 15mg of prednisolone (or equivalent) daily or equavilent were excluded, as we believed that such potent immunosuppression may confound our immunological analyses. The selected patients were contacted by one of the researchers (EB). Study information, a consent form and fatigue and quality of life questionnaires were mailed to all participants that showed initial interest. The patients that reported symptoms of fatigue and an MFS score ≥ 14 were included

in the "fatigued" group and the patients without symptoms of mental fatigue and an MFS score ≤10 points were included in the control group. The inclusion and exclusion criteria are listed in supplemental table 1. Patients with significant depression according to clinical assessment and the hospital anxiety and depression scale (HAD) were excluded(1). After inclusion, all cognitive testing was performed by one researcher (EB). Brain Magnetic Resonance Imaging (MRI) was performed on all participants, in order to exclude other causes of mental fatigue or cognitive dysfunction and signs of increased intracranial pressure, before lumbar puncture (LP) and blood sampling. A study flow chart is depicted in supplemental figure 1.

Clinical data collection

Occupational status and education was assessed by patient reports. Data on medical history, indication for transplant, previous treatments, transplantation procedure and post-transplant complications were obtained from hospital medical records.

Measurement of fatigue, quality of life, depression and anxiety

For measuring the extent of mental fatigue, and for classification of participants, the MFS was used(2). The MFS is a validated self-reporting questionnaire, in the Swedish language, that incorporates affective, cognitive and sensory symptoms, duration of sleep and daytime variation(2). For each question the patient rates his or her symptoms from 0 to 3 with increments of 0.5, with 0 corresponding to no symptom, and 3 corresponding to maximum intensity. The Fatigue Severity Scale (FSS) was applied to assess the impact of fatigue on different aspects of functioning(3, 4). It consists of 9 questions, based on which the patient grades his or her symptoms on a scale from 1 to 7. Quality of life was measured using the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) scale(5).

Depression and anxiety were assessed using the HAD(1). The psychometric properties of the instruments used are listed in supplemental table 2.

Assessment of cognitive function

To analyze cognitive function we selected five tests (supplemental table 3) with available, demographically corrected, normative data from the computer-based Cambridge Neuropsychological Test Automated Battery (CANTAB)(6). The CANTAB battery is language independent and culture free, and has been standardized on elderly and younger populations(6, 7). The selected tests are sensitive to mainly frontal and temporal lobe dysfunction and evaluate the following domains: executive function, visual memory and attention/processing speed(8, 9). This allowed for a clinically convenient test duration (30-40 minutes), that does not require previous neuropsychological training of the test administrator. Premorbid intelligence quotient(IQ)-levels were estimated using the Swedish version of the National Adult Reading Test (SWE-NART)(10).

Z-scores for each individual test were derived from normative data, and matched for age and SWE-NART score. The Z-scores were converted to a deficit score (DS) ranging from 0 (no impairment) to 5 (severe impairment). The DS were averaged to derive a Global Deficit Score (GDS), reflecting overall performance(11). Cognitive dysfunction was defined as GDS>0.5. Impairment on any individual test was defined as a Z-score≤-1.

Collection of CSF and peripheral blood samples

Paired cerebrospinal fluid (CSF) and peripheral blood samples were obtained from the participants. Twenty ml of CSF was collected by sterile LP. Seven ml of CSF was centrifuged at 400xg for 10 minutes at 4^{o}C and frozen in aliquots at -80^{o}C. The cell pellet was resuspended in pooled human AB plasma supplemented with 10% (v/v) dimethyl sulfoxide

(DMSO; Sigma-Aldrich Sweden AB. Stockholm, Sweden) and stored in liquid nitrogen. The remaining 13ml of CSF was sent directly for analysis. Blood was collected in heparinized tubes and peripheral blood mononuclear cells (PBMCs) isolated by centrifugation using Lymphoprep™ (Alere Technologies AS, Oslo, Norway). Separated cells were washed in phosphate buffered saline (PBS), centrifuged at 400xg and resuspended in pooled human AB plasma supplemented with 10% (v/v) DMSO for cryopreservation.

Flow cytometry analysis of PBMCs

Immunophenotyping of PBMCs was performed for comparative analysis with the CSF profiling. Cells were thawed and washed twice with RPMI media supplemented with 10% (v/v) fetal calf serum (ThermoFisher Scientific, Stockholm, Sweden). Cells were stained for 20 minutes at 4^{o}C. Supplemental table 4 lists all antibodies used. LIVE/DEAD™ fixable aqua dead cell stain was used to assess cell viability (ThermoFisher Scientific). Cells were run on an LSRFortessa™ (Becton Dickinson) and data were analyzed using FlowJo X software.

CSF protein analysis

Sample labelling

The samples were labelled at an adjusted protein concentration for 1 hour with scioDye 2. After 1 hour, the reaction was stopped by the addition of hydroxylamine. Excess dye was removed 30 minutes later and the buffer exchanged to PBS. All labelled protein samples were analysed immediately.

Sample incubation

The samples were analyzed on scioCD antibody microarrays (Sciomics) targeting 93 different CD surface markers and 25 cytokines/chemokines with 256 monoclonal antibodies. Each

antibody is represented on the array in 4 replicates. The arrays were blocked with scioBlock (Sciomics) on a Hybstation 4800 (Tecan, Austria), and the samples were incubated on the arrays. After incubation for 3 hours, the slides were thoroughly washed with 1x PBS supplemented with 0.05% w/v Tween®-20 and 0.05% w/v Triton™ X-100 (PBSTT), rinsed with 0.1x PBS, as well as, with distilled water and subsequently dried with nitrogen.

Data acquisition

Slide scanning was conducted using a Powerscanner (Tecan, Austria) with identical instrument laser power and adjusted photomultiplier tube (PMT) settings. Spot segmentation was performed with GenePix Pro 6.0 (Molecular Devices, Union City, CA, USA).

Statistical analysis

Patient characteristics, cognitive function, clinical CSF and flow cytometry parameters

For continuous variables, normality was tested using the Shapiro-Wilk test. Data with non-parametric distribution was compared using a Wilcoxon rank-sum or Kruskal-Wallis test with post-hoc analysis using Dunn's test with Benjamini-Hochberg correction. Normally distributed data was compared using a Student's t-test or one-way analysis of variance (ANOVA). Categorical variables were compared using Fisher's exact test. Linear regression models were used to analyze the correlation between fatigue or cognitive dysfunction and immune cell subsets and other tested parameters in the CSF and peripheral blood. The immune cell subsets and CSF parameters were dependent variables. Age, sex, time from transplant, fatigue and cognitive dysfunction were used as independent variables. All statistical tests were considered significant at $p<0.05$. Since this was a pilot study, the results were considered hypothesis-generating and no further correction for multiple analyses was conducted. To estimate the required size of a follow up study, power calculations were

performed for selected outcome variables using mean differences and standard deviations obtained in the study (supplemental table 5). Statistical analysis was performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Protein microarray data

Acquired raw data were analyzed using the linear models for microarray data (LIMMA) package of R-Bioconductor after uploading the median signal intensities. For normalization, a Cyclic Loess normalization was applied. For analysis of the samples a one-factorial linear model was fitted with LIMMA resulting in a two-sided t-test or F-test based on moderated statistics. All presented p values were adjusted for multiple testing by controlling the false discovery rate according to Benjamini and Hochberg. Proteins were defined as differential for $|\text{logFC}| > 0.25$ and an adjusted p value < 0.05. In addition, to generate hypotheses for future studies, we examined the proteins that were statistically significantly different when no control for false discovery rate was applied, in connection with the flow cytometry data, for any pattern that might indicate an immunological mechanism causing fatigue or cognitive dysfunction.

Differences in protein abundance between different samples or sample groups are presented as log-fold changes (logFC) calculated for the basis 2. In a study comparing samples versus control a logFC = 1 means that the sample group had on average a $2^1 = 2$-fold higher signal as the control group. logFC = −1 stands for $2^{-1} = 1/2$ of the signal in the sample as compared to the control group.

Supplemental results

Hypothesis-generating analysis of protein microarray and flow cytometry data

The linear regression analysis of the flow cytometry data suggest that fatigue is associated with a statistically significant lower proportion of B-cells and higher proportion of T-cells in blood (as % of lymphocytes), while cognitive dysfunction is associated with lower proportion of B-cells in CSF, higher proportion of B-cells in blood and higher proportion of double negative T-cells (CD4-CD8-, as % of T-cells) in both blood and CSF (supplemental table 10).

Further, we examined the cytokines in the microarray that were significantly different between fatigued patients and controls, as well as between patients with and without cognitive dysfunction, when adjustment for multiple comparisons was removed (supplemental table 11). This sub-analysis detected statistically significantly lower levels of interferon (IFN) α, interleukin (IL) 8 and Monocyte Chemotactic Protein (MCP) 3 in fatigue patients compared to controls. IL1β was detected twice, both as increased and decreased in fatigued patients. Therefore, cautiously we have chosen not to include that data. Taken together, these findings, as well as, the lower amount of B-cells in the blood, are not supportive of inflammation as a cause of fatigue. Further validation with more intricate flow cytometry panels may help to delineate the phenotype of the increased T-cell levels detected in blood.

The patients with cognitive dysfunction on the other hand have increased double negative T-cells in CSF and blood, a cell subset that has been associated with autoimmune disease and CNS inflammation after stroke(12, 13). Cytokine analysis revealed increased levels of IL37, a cytokine considered to be anti-inflammatory, but also associated with autoimmune disease(14).

Given the limited study size and multiple comparisons performed, the present results must be interpreted with caution. Nevertheless, we believe that our findings indicate a biologic difference between patients with fatigue alone and patients with fatigue and cognitive dysfunction. This finding may have implications for treatment and should be further studied in larger cohorts.

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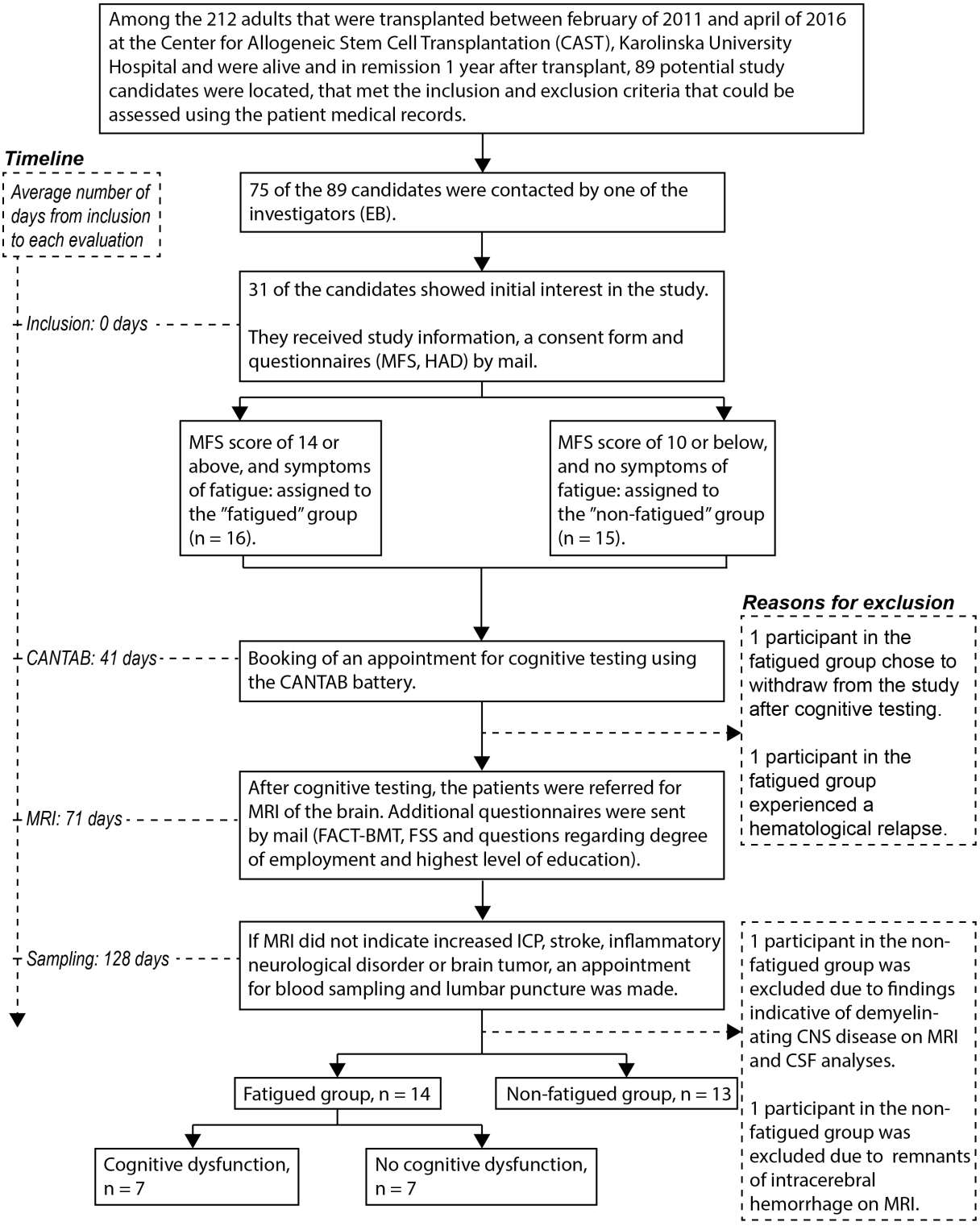
Supplemental figure 1: Study flowchart.



Abbreviations: MFS: Mental Fatigue Scale, HAD: Hospital Anxiety and Depression scale, CANTAB: Cambridge Neuropsychological Test Automated Battery, FACT-BMT: Functional Assessment of Cancer Therapy – Bone Marrow Transplant, CNS: Central Nervous System, MRI: Magnetic Resonance Imaging

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Supplementary tables

Supplemental table 1: Inclusion and exclusion criteria

#	**Inclusion criteria**	**Exclusion criteria**
1	≥ 18 years old	History of intracranial infection
2	Underwent allogeneic HSCT for hematologic malignancy ≥12months and ≤5 years ago.	History of intrathecal chemotherapy
3		Treated with total body irradiation as part of conditioning regiment for HSCT.
4		Current active or chronic neurological or psychiatric disorder, such as stroke, inflammatory neurological disease, schizophrenia, severe depression, suicide tendencies, anorexia nervosa, severe mood swings, bipolar disorder or any type of dementia or other degenerative neurological disease.
5		Current use of antipsychotic drugs, tricyclic antidepressants (in higher doses used for treating depression), high doses of benzodiazepines (20mg of diazepam daily or equivalent), high doses of opioids (30mg of morphine or equivalent daily).
6		Current or history of substance abuse.
7		Current medication with steroids, ≥15mg of prednisolone or equivalent.
8		MRI showing signs of elevated intracranial pressure or increased risk of cerebral herniation following lumbar puncture.
9		Increased risk of bleeding, i.e. thrombocytes < 50 x 10^9/L, Prothrombin Time, International Normalized Ratio > 1.4, complicating lumbar puncture.
10		Skin infection at the location for lumbar puncture (above the L3/L4 or L4/L5 lumbar vertebra).
11		Magnetic implant, or implanted device disturbing MRI examination.

Supplemental table 2: Psychometric properties of the instruments used for fatigue and quality of life measurements

Test	Reliability	Validity	Reference
MFS	Cronbach's Alpha: 0.944 (TBI, MS, whiplash, stroke and stress/ burnout)	Healthy control group reported significantly lower results compared to TBI, stress/burnout, whiplash, stroke and MS subjects. Higher MFS score correlates to lower performance on objective cognitive tests (TMT, digit symbol coding, digit span, verbal fluency, reading speed).	(2, 15)
FSS	Cronbach's Alpha: 0.81 (MS) 0.89 (SLE), 0.88 (healthy)	Correlation to VAS scale: $r = 0.68$, $p < 0.0001$	(4)
FACT-BMT	Cronbach's Alpha: 0.89-0.92 (before to 100 days post aHSCT)	Sensitive to change in performance status. Correlates with results from Brief POMS, CES-D and MOS-SS.	(5)
HADS	Cronbach's Alpha: 0.68-0.93 (HADS-A), 0.67-0.90 (HADS-D)	Correlates with BDI, GHQ, STAI, MADRS, CAS, HAMA, SCL-90. Sensitivity and specificity approximately 0.8. Medium to strong correlations (r=0.60-0.80)	(16)
SWE-NART	Cronbach's Alpha: 0.937 No significant difference between scores at baseline and after a 2 year follow-up. Retest reliability coefficient = 0.92	No significant difference in SWE-NART score between healthy controls and patients with Alzheimers Disease. No correlation of current mental ability (MMSE score) and SWE-NART score. NART-SWE score correlates with IQ levels in healthy controls, measured using GAI.	(10)

Abbreviations: MFS: Mental Fatigue Scale, FSS: Fatigue Severity Scale, FACT-BMT: Functional Assessment of Cancer Therapy – Bone Marrow Transplantation, HADS: Hospital Anxiety and Depression Scale, HADS-A: HADS-Anxiety, HADS-D: HADS-Depression, TBI: Traumatic Brain Injury, MS: Multiple Sclerosis, aHSCT: Allogeneic Hematopoietic Stem Cell Transplantation, TMT: Trail Making Test, VAS: Visual Analogue Scale, Brief POMS: Brief Profile of Mood States – Total Mood Disturbance Scale, CES-D: Center of Epidemiologic Studies – Depression, MOS-SS: Medical Outcomes Study – Social Support, BDI: Beck Deperssion Inventory, CAS; Clinical Anxiety Scale, HAMA: Hamilton Anxiety Scale, MADRS: Montgomery Asberg Depression Rating Scale, SCL-90: Symptom Checklist 90, STAI: Spielberger State-Trait Anxiety Inventory, GHQ: General Health Questionnaire, SWE-NART: Swedish version of the National Adult Reading Test, GAI: General Ability Index (short form of WAIS-III)

Supplemental table 3: Selected cognitive tests from CANTAB

Test	**CNS Function tested**	**Sensitive to dysfunction in the following cortical areas**
Intra-Extra Dimensional Set Shift (IED)	Executive function	Frontal lobe(8)
Paired Associates Learning (PAL)	Visual memory	Medial temporal lobe / hippocampus(9)
Pattern Recognition Memory (PRM)	Visual memory	Medial temporal lobe / hippocampus(9)
Reaction Time (RTI)	Attention / processing speed	Motor cortex
Stockings of Cambridge (SOC)	Executive function	Frontal lobe(8)

Abbreviations: CANTAB: Cambridge Neuropsychological Test Automated Battery, CNS: Central Nervous System

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Supplemental table 4: Flow cytometry antibodies

Cerebrospinal fluid antibodies[a]			
Antigen	**Fluorochrome (panel 1)**		**Fluorochrome (panel 2)**
CD19	FITC		FITC
CD25	PE		PE
CD3	PerCp-Cy5.5		APC
CD45RO	PE-Cy7		PE-Cy7
CD56	APC		V500
CD8	APC-H7		APC-H7
CD4	PB		V450
CD45	V500		
CD127			PerCP-Cy5.5
Peripheral blood antibodies			
Antigen	**Fluorochrome**	**Clone**	**Company**
CD3	PerCp-Cy5.5	OKT3	Biolegend
CD4	PE-cy5	OKT4	Biolegend
CD8	AF 488	RPA-T8	Biolegend
CD14	PerCp Cy5.5	HCD14	Biolegend
CD16	PE-CF594	3G8	BD Biosciences
CD19	BV786	SJ25C1	BD Biosciences
CD25	PE-Cy7	M-A251	BD Biosciences
CD27	APC	M-T271	Biolegend
CD33	PE	P67.6	Biolegend
CD45RA	APC-Cy7	HI100	Biolegend
CD56	BV605	NCAM	Biolegend
HLA-DR	APC-Cy7	L243	Biolegend
CXCR4	APC	12G5	BD Biosciences
CD11b	FITC	M1/70	Biolegend
LIVE/DEAD™ Fixable Dead Cell Stain	V525		Invitrogen

[a]Analysis performed by the Department of Pathology, Karolinska University Hospital.
Abbreviations: PB: Pacific Blue, PE: Phycoerythrin, Cy: Cyanine dye, FITC: Fluorescein

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Isothiocyanate, PerCP: Peridinin-chlorophyll-protein complex, APC: Allophycocyanin, CD: Cluster of Differentiation, AF: Alexa Fluor, BV: Brilliant Violet

Supplemental table 5: Power calculations for t-test comparison of selected parameters between fatigued and non-fatigued patients

Parameter	Mean difference	SD	Power	N[a]
FACT BMT Total score	35.4	16	1	6
FSS score	2.89	1.55	0.995	8
GDS	0.514	0.31	0.982	9
Working/studying % of full time	6.26	42.6	0.065	975
Blood flow cytometry subsets				
T-cells (CD3+)	7.46	14.5	0.244	60
B-cells (CD19+)	1.91	8.73	0.0833	331
DN T-cells (CD3+CD4-CD8-)	0.682	5.94	0.0591	1192
CSF flow cytometry subsets				
NK-cells (CD3-CD56+)	1.15	2.74	0.18	90
T-cells (CD3+)	7.21	32.6	0.0843	321
DN T-cells (CD3+CD4-CD8-)	0.231	2.19	0.0576	1419
B-cells (CD19+)	0.00927	0.573	0.0502	60009

The power calculations are based on the actual means and SD in the study.
[a]The number of subjects in each group required to achieve 80% power with a significance level of 0.05.
Abbreviations: SD: Standard deviation, FACT BMT: Functional Assessment of Cancer Therapy - Bone Marrow Transplantation, FSS: Fatigue Severity Scale, GDS: Global Deficit Scale, DN T-cells: Double Negative T-cells, NK-cells: Natural Killer cells

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Supplemental table 6: Clinical cerebrospinal fluid parameters

Measurement	No Fatigue	Fatigue	p	CD[a]	No CD[a]	p
Inflammation and blood brain barrier damage						
Leucocytes	1.77 (0 - 5)	1.31 (0 - 4)	0.38[#]	0.86 (0 - 2)	1.79 (0 - 5)	0.12[#]
Mononuclear cells	1.77 (0 - 5)	1.31 (0 - 4)	0.38[#]	0.86 (0 - 2)	1.79 (0 - 5)	0.12[#]
Polynuclear cells	0 (0 - 0)	0 (0 - 0)	NA	0 (0 - 0)	0 (0 - 0)	NA
Albumin	255 (175 - 423)	211 (123 - 545)	0.09[#]	229 (123 - 545)	236 (141 - 423)	0.35[#]
CSF/P Albumin ratio	6.28 (4 - 9.8)	5.13 (3 - 13.1)	0.07[#]	5.49 (3 - 13.1)	5.82 (3.4 - 9.8)	0.25[#]
IgG-index	0.46 (0.43 - 0.48)	0.46 (0.38 - 0.53)	0.83[†]	0.47 (0.42 - 0.53)	0.45 (0.38 - 0.49)	0.44[†]
CXCL13	16.9 (0 - 100)	7.69 (0 - 55)	0.24[#]	4.43 (0 - 22)	15.11 (0 - 100)	0.42[#]
Metabolism						
Lactate	1.64 (1.4 - 2)	1.71 (1.3 - 2.1)	0.43[†]	1.7 (1.3 - 2)	1.66 (1.4 - 2.1)	0.71[†]
Neurodegeneration						
Phospho-Tau	57.4 (31 - 89)	48.3 (19 - 76)	0.15[†]	45.57 (19 - 76)	55.53 (31 - 89)	0.26[†]
Tau	267 (155 - 482)	225 (101 - 410)	0.25[†]	214 (101 - 410)	258 (130 - 482)	0.37[†]
Beta amyloid	1222 (858 - 1610)	1132 (766 - 1400)	0.28[†]	1109 (811 - 1400)	1202 (766 - 1610)	0.29[†]
NfL	792 (460 - 1360)	718 (280 - 1640)	0.6[†]	647 (280 - 1020)	791 (370 - 1640)	0.32[†]
S100B	3.17 (1.6 - 4.2)	3.27 (1.5 - 10)	0.18[#]	3.92 (1.5 - 10)	2.95 (1.6 - 4.2)	0.77[#]

Data is displayed as mean (range). [a]Cognitive dysfunction is defined as a global deficit score > 0.5 on the CANTAB testing. [b]Adjusted for age, sex and time since transplant using linear regression. [#]Wilcoxon Rank Sum Test. [†]T-test. Abbreviations: CD: Cognitive Dysfunction, NA: Not applicable, NfL: Neurofilament Light Chain, CXCL: C-X-C motif Ligand

Supplemental table 7: Number of patients with clinical CSF parameters outside of the normal range.

Parameter	Fatigue	No fatigue	P-value[#]
CSF IgG	2	1	0.54
CSF Albumin	0	1	NA
CSF/P-Albumin	1	2	0.54
S100B	3	8	0.047
CXCL13	4	5	0.68
IL8	1	0	NA
Tau	1	2	0.54
Phospho-Tau	2	5	0.54
NfL	1	3	0.28

[#]Chi-square test. Abbreviations: CSF=cerebrospinal fluid, NfL: Neurofilament Light Chain,

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Supplemental table 8: Cerebrospinal fluid flow cytometry analyses

Cell subset	No Fatigue	Fatigue	p	No CD[a]	CD[a]	p
T-cells						
CD3+ CD19-	46.12 (0.516 - 86.5)	53.33 (0.936 - 97.6)	0.54 #	55.02 (0.516 - 97.6)	35.34 (0.936 - 84.4)	0.13 #
CD3+ CD56- CD45RO+	85.58 (70.8 - 90.4)	84.82 (73.1 - 95.3)	0.77 †	84.86 (70.8 - 91.2)	86.11 (73.3 - 95.3)	0.72 †
CD3+ CD56- CD45RO-	14.42 (9.60 - 29.2)	15.18 (4.7 - 26.9)	0.77 †	15.14 (8.8 - 29.2)	13.89 (4.7 - 26.7)	0.72 †
CD3+ CD19- CD4+	60.21 (37.6 - 74.1)	55.67 (0 - 73.5)	0.8#	60.66 (37.6 - 74.1)	50.54 (0 - 73.5)	0.42 #
CD3+ CD19- CD4+ CD25+	29.28 (8.17 - 45.6)	23.95 (10.7 - 51.2)	0.33 †	27.0 (8.17 - 51.2)	26.35 (16.5 - 44.1)	0.92 †
CD3+ CD56- CD4+ CD45RO+	95.26 (89.5 - 100)	94.48 (86.3 - 99)	0.6†	95.17 (89 - 100)	94 (86.3 - 98.8)	0.62 †
CD3+ CD56- CD4+ CD45RO-	4.74 (0 - 10.5)	5.52 (1 - 13.7)	0.6†	4.83 (0 - 11)	6 (1.2 - 13.7)	0.62 †
CD3+ CD19- CD8+	35.57 (22.2 - 54.1)	40.22 (24.4 - 94.3)	0.72 #	35.57 (22.2 - 54.1)	44.2 (24.4 - 94.3)	0.73 #
CD3+ CD19- CD8+ CD25+	3.59 (0 - 10.6)	5.29 (0.794 - 24.2)	0.64 #	3.4 (0 - 10.6)	7.26 (1.44 - 24.2)	0.22 #
CD3+ CD56- CD8+ CD45RO+	71.82 (41.5 - 86.3)	70.79 (43.9 - 97)	0.86 †	69.09 (41.5 - 86.4)	77.3 (51.4 - 97)	0.3†
CD3+ CD56- CD8+ CD45RO-	28.18 (13.7 - 58.5)	29.21 (3 - 56.1)	0.86 †	30.91 (13.6 - 58.5)	22.7 (3 - 48.6)	0.3†
CD3+ CD19- CD4- CD8-	3.06 (0.985 - 9.4)	3.29 (0.781 - 6.8)	0.96 #	2.73 (0.975 - 9.4)	4.4 (0.781 - 6.8)	0.09 #
CD4+/CD8+ ratio	1.92 (0.71 - 3.34)	1.78 (0 - 2.94)	0.69 †	1.92 (0.71 - 3.34)	1.66 (0 - 2.94)	0.6†
B-cells						
CD19+	0.54 (0 - 1.42)	0.55 (0 - 2.43)	0.56 #	0.57 (0 - 2.43)	0.49 (0.00111 - 1.26)	0.82 #

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NK-cells						
CD3- CD56+	4.36 (0.741 - 10.4)	3.21 (0.312 - 10.2)	0.12 [#]	3.94 (0.533 - 10.4)	3.39 (0.312 - 10.2)	0.25 [#]
CD3- CD56+ CD25+	15.01 (0.84 - 40.4)	13.5 (0 - 29.6)	0.73 [†]	14.83 (0 - 40.4)	12.79 (3.92 - 29.6)	0.68 [†]
NKT-cells						
CD3+ CD56+	19.72 (0.153 - 59.3)	19.3 (0.0918 - 77.8)	0.38 [#]	16.47 (0.153 - 59.3)	27.75 (0.0918 - 77.8)	1[#]
CD3+ CD56+ CD8+	24.83 (9.09 - 45.4)	22.03 (0 - 45.5)	0.56 [†]	24.74 (9.09 - 45.5)	19.87 (0 - 44.8)	0.45 [†]
CD3+ CD56+ CD4+	70.06 (49 - 83.8)	72.04 (47.9 - 100)	0.69 [†]	69.83 (49 - 83.8)	74.37 (47.9 - 100)	0.52 [†]
CD3+ CD56+ CD4+ CD25+	36.22 (11.1 - 58.1)	28.71 (8.7 - 66.7)	0.32 [†]	32.3 (8.7 - 58.1)	34.23 (18.7 - 66.7)	0.83 [†]
CD3+ CD56+ CD4+ CD8+	3.27 (0.569 - 7.58)	3.21 (0 - 9.62)	0.95 [†]	3.63 (0.569 - 9.62)	2.2 (0 - 5.27)	0.13 [†]
CD3+ CD56+ CD4- CD8-	2 (0 - 4.26)	2.71 (0 - 7.69)	0.68 [#]	1.92 (0 - 4.76)	3.54 (0 - 7.69)	0.2[#]

Data is displayed as mean (range). [a]Cognitive dysfunction is defined as a global deficit score > 0.5 on the CANTAB testing. [#]Wilcoxon Rank Sum Test (non-parametric distribution according to the Shapiro-Wilk test). [†]T-test (parametric distribution according to the Shapiro-Wilk test). Abbreviations: CD: Cognitive Dysfunction, NK: Natural Killer, NKT: Natural Killer T cell

Supplemental table 9: Peripheral blood flow cytometry results

Cell subset	No Fatigue	Fatigue	p	No CD[a]	CD[a]	p
Monocytes						
CD14+ CD16+	6.9 (1.5 - 22)	7.54 (1.26 - 13.9)	0.31 #	6.71 (1.26 - 22)	8.61 (5.21 - 13.9)	0.15 #
CD14+ CD16-	70.24 (46.1 - 87.6)	66.31 (56 - 86.6)	0.37 †	69.01 (46.1 - 87.6)	66.29 (56 - 76.2)	0.53 †
CD11b+ Monocytes	78.04 (57.5 - 90.9)	75.82 (67.1 - 87.6)	0.48 †	76.68 (57.5 - 90.9)	77.59 (68.9 - 81.5)	0.74 †
B-cells						
CD19+ CD3-	11.48 (2.26 - 26.9)	9.58 (1.09 - 38.3)	0.31 #	9.18 (1.09 - 26.9)	14.21 (2.08 - 38.3)	0.3#
NK-cells						
CD56+ CD3-	16.17 (2.89 - 39.61)	13.33 (1.47 - 30.61)	0.45 †	14.25 (1.47 - 39.61)	16.1 (6.01 - 30.61)	0.66 †
CD56bright CD16-	6.35 (0.962 - 13.7)	6.12 (0.833 - 11.7)	0.89 †	6.58 (0.962 - 13.7)	5.29 (0.833 - 11.6)	0.49 †
CD56dim CD16+	91.98 (84.7 - 98.7)	91.88 (84.3 - 98.8)	0.96 †	91.55 (84.7 - 98.7)	92.97 (84.3 - 98.8)	0.54 †
NKT-cells						
CD3+ CD56+	3.57 (0.35 - 15.36)	4.08 (0.62 - 12.28)	0.44 #	3.47 (0.35 - 15.36)	4.81 (0.88 - 12.28)	0.36 #
CD3+ CD56+ CD8+	51.1 (6.93 - 82.9)	52.31 (18.2 - 86.9)	0.9†	52.5 (6.93 - 86.9)	49.54 (18.2 - 77.7)	0.79 †
CD3+ CD56+ CD4+	13.12 (0.291 - 59.1)	10.37 (0.369 - 43.7)	0.32 #	14.48 (0.291 - 59.1)	4.32 (1.14 - 12.3)	0.06 #
CD3+ CD56+ CD4+ CD8+	2.06 (0 - 7.52)	1.39 (0 - 15)	0.12 #	2.26 (0 - 15)	0.29 (0 - 0.885)	0.17 #
T-cells						

CD3+ CD56-	52.92 (28.45 - 76.47)	60.38 (41.0848 - 90.7184)	0.2[†]	57.87 (28.45 - 90.72)	53.33 (41.08 - 73.55)	0.44 [†]
CD3+ CD56- CD45RA+ CD27+(Naive)	17.53 (2.41 - 39.8)	16.73 (3.96 - 50)	0.96 [#]	17.58 (2.41 - 46)	15.92 (3.96 - 50)	0.71 [#]
CD3+ CD56- CD45RA+ CD27- (TEMRA)	20.14 (3.5 - 59.5)	24.28 (3.11 - 69.3)	0.57 [#]	22.67 (3.11 - 69.3)	20.97 (4.36 - 42.9)	0.86 [#]
CD3+ CD56- CD45RA- CD27- (EM)	31.99 (13.9 - 51.9)	26.5 (9.19 - 50.3)	0.28 [†]	28.83 (10.1 - 51.9)	30.38 (9.19 - 50.3)	0.8[†]
CD3+ CD56- CD45RA- CD27+ (CM)	30.32 (6.14 - 48.8)	32.48 (6.69 - 58.5)	0.7[†]	30.91 (6.14 - 58.5)	32.74 (13.3 - 57.3)	0.77 [†]
CTL:s (CD8+ T-cells)						
CD3+ CD56- CD8+	38.03 (4.74 - 77.8)	46.85 (14 - 94.2)	0.32 [†]	42.35 (4.74 - 94.2)	42.66 (14 - 78.9)	0.98 [†]
CD3+ CD56- CD8+ CD25+	2.65 (0.761 - 6.4)	2.08 (0.614 - 4.11)	0.61 [#]	2.6 (0.761 - 6.4)	1.74 (0.614 - 3.87)	0.15 [#]
CD3+ CD56- CD8+ CD45RA+ CD27+(Naive)	22.46 (2.36 - 53.8)	20.39 (4.52 - 59.7)	0.76 [#]	22.96 (2.36 - 59.7)	17.26 (4.76 - 39.3)	0.47 [#]
CD3+ CD56- CD8+ CD45RA+ CD27- (TEMRA)	35.63 (6.35 - 70.5)	35.78 (9.09 - 71.6)	0.98 [†]	36.75 (6.35 - 71.6)	32.88 (9.09 - 57.3)	0.64 [†]
CD3+ CD56- CD8+ CD45RA- CD27- (EM)	21.32 (5.72 - 46)	21.16 (6.84 - 49.3)	0.84 [#]	19.15 (5.72 - 46)	26.92 (9.74 - 49.3)	0.27 [#]
CD3+ CD56- CD8+ CD45RA- CD27+ (CM)	20.58 (3.68 - 42.5)	22.66 (5.4 - 42.8)	0.64 [†]	21.14 (3.68 - 42.8)	22.93 (10.1 - 41.9)	0.74 [†]
Th-cells (CD4+ T-cells)						

CD3+ CD56- CD4+	53.9 (8.49 - 92.1)	44.62 (3.7 - 73.8)	0.3[†]	50.41 (3.7 - 92.1)	46.13 (16.6 - 71.3)	0.63 [†]
CD3+ CD56- CD4+ CD25+	10.4 (4.46 - 21.4)	10.88 (6.99 - 19.5)	0.78 [#]	10.63 (4.46 - 21.4)	10.67 (6.99 - 16.1)	1[#]
CD3+ CD56- CD4+ CD45RA+ CD27+(Naive)	13.15 (0.41 - 35.8)	12.49 (0.41 - 50.8)	0.88 [#]	12.58 (0.407 - 40.2)	13.48 (0.408 - 50.8)	0.91 [#]
CD3+ CD56- CD4+ CD45RA+ CD27- (TEMRA)	2.57 (0 - 14.7)	4.51 (0.285 - 20.5)	0.15 [#]	3.15 (0 - 15.2)	4.59 (0.539 - 20.5)	0.36 [#]
CD3+ CD56- CD4+ CD45RA- CD27- (EM)	45.52 (17.8 - 74.8)	37.22 (11.8 - 65)	0.28 [†]	42.97 (11.8 - 74.8)	37.04 (12.5 - 65)	0.51 [†]
CD3+ CD56- CD4+ CD45RA- CD27+ (CM)	38.75 (23.9 - 56.2)	45.78 (15.4 - 69.8)	0.2[†]	41.31 (23.9 - 64.2)	44.89 (15.4 - 69.8)	0.66 [†]
Ratio						
CD4+/CD8+ rato	3.18 (0.11 - 19.43)	1.56 (0.034 - 5.09)	0.41 #	2.6 (0.039 - 19.43)	1.76 (0.21 - 5.09)	0.91 #
Double positive / Double negative T-cells						
CD3+ CD56- CD4+ CD8+	0.75 (0.057 - 3.54)	0.52 (0.028 - 1.6)	0.76 [#]	0.67 (0.051 - 3.54)	0.55 (0.028 - 1.6)	0.49 [#]
CD3+ CD56- CD4- CD8-	7.33 (2.21 - 14.4)	8.01 (1.02 - 29.3)	0.82 [#]	6.57 (1.02 - 14.4)	10.66 (4.24 - 29.3)	0.24 [#]

Data is displayed as mean (range). [a]Cognitive dysfunction is defined as a global deficit score > 0.5 on the CANTAB testing. [#]Wilcoxon Rank Sum Test (non-parametric distribution according to the Shapiro-Wilk test). [†]T-test (parametric distribution according to the Shapiro-Wilk test). Abbreviations: CD: Cognitive Dysfunction, NK: Natural Killer, NKT: Natural Killer T, EM: Effector Memory, CM: Central Memory, TEMRA: Terminally differentiated effector memory cells re-expressing CD45RA

Supplemental table 10: Linear regression analysis of CSF and blood cell data

Parameter	Age[a]	p	Sex[b]	p	Time from aHSCT to inclusion [c]	p	Fatigue[d]	p	CD[e]	p
CSF clinical parameters										
Inflammation and blood brain barrier damage										
Leucocytes	0.02	0.18	-0.87	0.10	-0.01	0.63	0.02	0.98	-0.95	0.18
Mono-nuclear cells	0.02	0.18	-0.87	0.10	-0.01	0.63	0.02	0.98	-0.95	0.18
Polynuclear cells	0.00	-	0.00	-	0.00	-	0.00	-	0.00	-
Albumin	1.57	0.20	72.30	0.06	2.07	0.09	-49.90	0.30	32.10	0.54
CSF/P Albumin ratio	0.05	0.10	1.67	0.08	0.05	0.11	-1.08	0.36	0.52	0.68
IgG-index	0.00	0.51	-0.01	0.44	0.00	0.98	-0.02	0.32	0.02	0.19
CXCL13	0.46	0.16	-12.20	0.23	0.00	0.99	-4.95	0.68	-7.31	0.58
Metabolism										
Lactate	0.01	0.016*	0.00	0.96	0.00	0.85	0.12	0.26	-0.04	0.75
Neurodegeneration										
Phospho-Tau	-0.32	0.16	1.14	0.87	0.08	0.72	-7.50	0.37	-5.20	0.57
Tau	-1.82	0.17	-2.32	0.95	0.64	0.62	-41.00	0.41	-18.10	0.74
Beta amyloid	-7.95	0.0009*	-38.20	0.55	-6.87	0.003*	-116.00	0.15	-10.70	0.90
NFL	14.50	0.0004*	340.00	0.004*	-1.20	0.72	132.00	0.30	-221.00	0.14

S100B	0.01	0.79	1.96	0.08	-0.04	0.30	-0.29	0.84	0.80	0.61
CSF Flow cytometry										
T-cells (CD3+CD56-)										
CD3+ CD19-	-0.29	0.50	-7.32	0.58	0.01	0.98	25.00	0.14	-37.40	0.047*
CD45RO+	0.11	0.25	2.68	0.35	-0.05	0.57	-1.10	0.75	2.32	0.54
CD45RO-	-0.11	0.25	-2.68	0.35	0.05	0.57	1.10	0.75	-2.32	0.54
CD4+	-0.08	0.72	-5.24	0.46	0.26	0.27	-0.16	0.99	-10.80	0.27
CD4+ CD25+	0.10	0.57	3.64	0.53	-0.29	0.12	-6.47	0.36	5.75	0.47
CD4+ CD45RO+	0.05	0.31	3.65	0.02*	-0.04	0.41	0.73	0.67	-1.52	0.45
CD4+ CD45RO-	-0.05	0.31	-3.65	0.02*	0.04	0.41	-0.73	0.67	1.52	0.45
CD8+	0.10	0.65	5.73	0.40	-0.31	0.16	1.79	0.83	8.32	0.36
CD8+ CD25+	0.07	0.29	3.29	0.13	0.00	0.98	0.10	0.97	4.47	0.14
CD8+ CD45RO+	0.23	0.24	6.50	0.28	-0.21	0.28	-5.91	0.42	13.10	0.11
CD8+ CD45RO-	-0.23	0.24	-6.50	0.28	0.21	0.28	5.91	0.42	-13.10	0.11
CD4- CD8-	-0.03	0.31	-0.61	0.49	0.03	0.27	-1.36	0.21	2.49	0.04*
CD4+/CD8+ ratio	-0.01	0.54	-0.49	0.21	0.02	0.15	-0.16	0.74	-0.21	0.69
B-cells (CD19+)										
CD19+	0.01	0.37	-0.26	0.30	0.01	0.22	0.07	0.83	-0.14	0.67
NK-cells (CD3-CD56+)										
CD3- CD56+	0.09	0.023*	-0.83	0.44	0.01	0.70	-1.03	0.44	0.17	0.90
CD25+	0.02	0.87	-8.11	0.06	-0.23	0.10	-1.07	0.83	-1.85	0.75

NKT-cells (CD3+CD56+)										
CD3+ CD56+	0.33	0.26	-4.93	0.58	0.08	0.79	-9.37	0.40	17.60	0.16
CD8+	0.00	0.98	3.36	0.54	0.08	0.66	0.37	0.96	-5.12	0.48
CD4+	0.02	0.92	-1.52	0.78	-0.11	0.55	-0.94	0.89	5.33	0.48
CD4+ CD25+	0.24	0.33	8.58	0.27	-0.35	0.17	-11.00	0.25	12.80	0.23
CD4+ CD8+	0.00	0.90	-0.54	0.58	0.02	0.63	1.04	0.39	-2.19	0.10
CD4- CD8-	-0.01	0.62	-1.10	0.19	0.01	0.70	-0.57	0.58	1.93	0.09
Blood flow cytometry										
Monocytes										
CD14+ CD16+	0.08	0.19	-1.06	0.58	0.02	0.76	-0.33	0.89	2.13	0.41
CD14+ CD16-	-0.11	0.47	6.91	0.15	-0.09	0.54	-3.12	0.59	-0.21	0.97
CD11b+	-0.06	0.56	5.81	0.08	-0.14	0.19	-3.43	0.39	3.71	0.40
B-cells (CD19+CD3-)										
CD19+ CD3-	-0.18	0.11	-3.05	0.37	0.08	0.45	-8.99	0.04*	10.70	0.03 *
NK-cells (CD56+CD3-)										
CD56+ CD3-	0.16	0.23	1.49	0.71	-0.05	0.73	-4.83	0.34	5.45	0.32
CD56bright CD16-	-0.08	0.17	-2.66	0.13	0.04	0.49	-0.26	0.90	-1.36	0.55
CD56dim CD16+	0.11	0.10	3.41	0.10	-0.05	0.43	-0.02	1.00	1.78	0.51
NKT-cells (CD56+CD3+)										
CD3+ CD56+	0.02	0.70	1.01	0.55	0.00	0.95	-0.02	0.99	1.43	0.53
CD8+	-0.39	0.24	8.97	0.37	0.34	0.29	3.99	0.74	-6.26	0.64

CD4+	0.27	0.17	-2.91	0.62	-0.09	0.63	5.30	0.47	-13.50	0.10
CD4+ CD8+	0.07	0.15	1.64	0.24	0.04	0.43	1.34	0.43	-2.82	0.14
T-cells (CD56-CD3+)										
CD56- CD3+	-0.31	0.11	2.73	0.63	-0.09	0.64	14.50	0.048*	-14.40	0.07
CD45RA+ CD27+ (Naive)	-0.52	0.004*	-11.70	0.03*	0.14	0.39	-5.25	0.38	0.69	0.92
CD45RA+ CD27- (TEMRA)	-0.01	0.96	18.00	0.02*	-0.36	0.11	11.70	0.18	-8.23	0.38
CD45RA- CD27- (EM)	0.36	0.04*	3.78	0.45	-0.16	0.32	-7.14	0.25	7.24	0.29
CD45RA- CD27+ (CM)	0.17	0.36	-10.10	0.08	0.39	0.039*	0.70	0.92	0.34	0.96
CTL:s (CD56-CD3+CD8+)										
CD56- CD3+ CD8+	0.01	0.97	24.90	0.007*	-0.11	0.69	18.90	0.08	-11.30	0.32
CD25+	-0.02	0.28	-0.44	0.50	0.03	0.23	-0.39	0.63	-0.69	0.44
CD45RA+ CD27+ (Naive)	-0.46	0.026*	-15.20	0.019*	0.33	0.10	-4.27	0.56	-4.49	0.58
CD45RA+ CD27- (TEMRA)	0.05	0.84	12.90	0.11	-0.40	0.12	6.53	0.49	-6.97	0.50
CD45RA- CD27- (EM)	0.28	0.09	7.55	0.13	-0.18	0.26	-3.69	0.54	11.20	0.10
CD45RA- CD27+ (CM)	0.14	0.38	-5.30	0.27	0.25	0.11	1.44	0.80	0.24	0.97
Th-cells (CD56-CD3+CD4+)										

CD56-CD3+ CD4+	0.15	0.61	-22.70	0.016*	0.02	0.93	-14.90	0.17	4.95	0.67
CD25+	-0.06	0.27	-2.23	0.22	0.01	0.84	-0.11	0.96	-0.06	0.98
CD45RA+ CD27+ (Naive)	-0.45	0.017*	-10.70	0.06	0.03	0.88	-6.62	0.32	4.48	0.54
CD45RA+ CD27- (TEMRA)	0.01	0.86	-0.81	0.73	-0.10	0.19	1.78	0.54	0.39	0.90
CD45RA- CD27- (EM)	0.26	0.34	12.00	0.15	-0.33	0.22	-4.09	0.68	-1.75	0.87
CD45RA- CD27+ (CM)	0.18	0.31	-0.53	0.92	0.40	0.031*	8.96	0.19	-3.14	0.67
Ratio										
CD4+/CD8+ rato	0.05	0.35	-2.57	0.11	0.01	0.92	-2.09	0.28	0.51	0.81
Double positive and double negative T-cells (CD56-CD3+)										
CD4+ CD8+	0.00	0.74	-0.11	0.75	0.02	0.09	-0.31	0.47	0.05	0.92
CD4- CD8-	-0.16	0.046*	-2.07	0.37	0.06	0.41	-3.73	0.19	6.29	0.050*

A linear regression model was fitted with each leucocyte subset as dependent variable and fatigue, cognitive dysfunction, age, sex and time from transplant as independent variables. The table lists the coefficients and p-values for all independent variables. [a]Male/Female, [b]Years, [c]Months, [d]Fatigue is defined as belonging to the fatigued study group, [e]Cognitive dysfunction is defined as a global deficit score > 0.5 on the CANTAB testing. Abbreviations: CD: Cognitive Dysfunction, NK: Natural Killer, NKT: Natural Killer T, EM: Effector Memory, CM: Central Memory, TEMRA: Terminally differentiated effector memory cells re-expressing CD45RA

Boberg E. *et al.* Persistent fatigue after allogeneic hematopoietic stem cell transplantation is associated with cognitive dysfunction, but not central nervous system inflammation.

Supplemental table 11: All CSF protein multiplex results.

			Fatigue vs no fatigue			Cognitive dysfunction vs no cognitive dysfunction		
ID[a]	**Protein**	**Ave Expr[b]**	**logFC[c]**	**p[d]**	**p_{adj}[e]**	**logFC[c]**	**P[d]**	**P_{adj}[e]**
sc_001	CD117	15,88	-0,05	0,28	0,94	-0,10	0,11	0,94
sc_002	PDL1	15,39	0,02	0,89	0,99	0,31	0,06	0,94
sc_003	PD1	14,64	0,02	0,90	0,99	0,38	0,10	0,94
si_001	CD1a	13,94	0,04	0,69	0,96	0,05	0,63	0,96
si_002	CD2	13,24	0,10	0,31	0,94	0,10	0,41	0,96
si_003	CD2	13,04	-0,01	0,91	0,99	-0,02	0,85	0,96
si_004	CD2	13,42	0,15	0,29	0,94	0,08	0,62	0,96
si_005	CD3	14,03	0,08	0,44	0,94	-0,02	0,85	0,96
si_006	CD3	14,44	-0,03	0,80	0,99	-0,22	0,11	0,94
si_007	CD3	14,54	-0,04	0,70	0,96	-0,30	0,01	0,75
si_008	CD4	13,27	0,03	0,67	0,96	-0,11	0,20	0,96
si_009	CD4	13,37	0,01	0,89	0,99	0,06	0,54	0,96
si_010	CD4	13,66	0,04	0,63	0,96	-0,10	0,35	0,96
si_011	CD4	13,07	0,05	0,50	0,96	0,02	0,81	0,96
si_012	CD4	12,84	-0,08	0,45	0,94	0,05	0,73	0,96
si_013	CD5	12,88	-0,02	0,92	0,99	0,08	0,67	0,96
si_014	CD5	14,11	-0,01	0,92	0,99	0,10	0,55	0,96
si_015	CD6	14,23	-0,02	0,86	0,99	0,06	0,72	0,96
si_016	CD6	13,04	-0,14	0,35	0,94	-0,04	0,82	0,96
si_017	CD7	14,72	0,04	0,71	0,96	0,00	0,98	0,99
si_018	CD7	14,19	-0,06	0,56	0,96	0,01	0,95	0,99
si_019	CD7	13,44	0,11	0,38	0,94	-0,09	0,51	0,96
si_020	CD7	14,25	0,02	0,94	0,99	0,05	0,88	0,96
si_021	CD8	14,78	-0,07	0,66	0,96	-0,31	0,09	0,94
si_022	CD8	14,18	0,07	0,35	0,94	-0,05	0,58	0,96
si_023	CD8	14,38	0,31	0,03	0,64	0,33	0,05	0,94
si_024	CD8	13,76	0,08	0,26	0,94	-0,01	0,94	0,98
si_025	CD9	14,09	0,15	0,31	0,94	0,06	0,73	0,96

si_026	CD9	14,15	0,02	0,87	0,99	0,02	0,87	0,96
si_027	CD10	13,83	0,02	0,84	0,99	0,03	0,76	0,96
si_028	CD10	14,41	0,01	0,89	0,99	-0,03	0,80	0,96
si_029	CD10	13,64	-0,04	0,79	0,99	0,07	0,73	0,96
si_030	CD10	14,59	0,04	0,76	0,99	0,19	0,23	0,96
si_031	CD11a	13,66	-0,05	0,65	0,96	0,03	0,81	0,96
si_032	CD11a	14,96	0,26	0,14	0,94	0,14	0,53	0,96
si_033	CD11a	13,04	0,03	0,63	0,96	-0,02	0,81	0,96
si_034	CD11b	13,97	-0,18	0,13	0,94	-0,47	0,00	0,21
si_035	CD11b	12,91	-0,07	0,30	0,94	0,00	0,97	0,99
si_036	CD11b	14,19	0,19	0,05	0,87	0,13	0,24	0,96
si_037	CD11c	13,58	-0,04	0,56	0,96	-0,11	0,21	0,96
si_038	CD13	13,91	-0,06	0,40	0,94	-0,03	0,70	0,96
si_039	CD14	13,64	0,05	0,61	0,96	0,06	0,58	0,96
si_040	CD14	13,74	0,05	0,56	0,96	-0,07	0,44	0,96
si_041	CD14	13,55	0,01	0,91	0,99	0,08	0,38	0,96
si_042	CD15	11,98	0,04	0,63	0,96	0,03	0,75	0,96
si_043	CD15	11,49	-0,02	0,84	0,99	0,04	0,69	0,96
si_044	CD15	14,17	0,07	0,59	0,96	0,07	0,65	0,96
si_046	CD16	12,99	-0,24	0,16	0,94	0,03	0,89	0,96
si_047	CD16	13,95	-0,04	0,68	0,96	0,08	0,56	0,96
si_048	CD16	15,16	0,01	0,90	0,99	0,07	0,50	0,96
si_049	CD17	13,71	0,00	1,00	1,00	-0,10	0,30	0,96
si_051	CD18	12,74	0,04	0,52	0,96	0,04	0,61	0,96
si_052	CD18	12,61	-0,02	0,84	0,99	-0,09	0,48	0,96
si_053	CD18	12,48	0,09	0,21	0,94	0,02	0,79	0,96
si_054	CD19	13,97	0,01	0,94	0,99	0,00	0,97	0,99
si_055	CD19	14,07	0,02	0,79	0,99	0,04	0,71	0,96
si_056	CD20	14,41	0,00	0,95	0,99	-0,11	0,14	0,96
si_057	CD20	12,23	-0,01	0,93	0,99	-0,05	0,66	0,96
si_058	CD20	15,88	-0,06	0,21	0,94	-0,11	0,06	0,94

si_059	CD21	13,12	0,02	0,73	0,97	0,04	0,60	0,96
si_060	CD22	13,81	0,13	0,11	0,94	0,17	0,09	0,94
si_061	CD22	13,73	-0,14	0,25	0,94	0,04	0,81	0,96
si_062	CD22	13,62	-0,37	0,02	0,52	-0,19	0,28	0,96
si_063	CD23	13,87	-0,10	0,43	0,94	-0,02	0,87	0,96
si_064	CD24	14,22	-0,11	0,31	0,94	0,09	0,47	0,96
si_065	CD25	13,55	0,04	0,61	0,96	-0,08	0,39	0,96
si_066	CD25	14,71	0,04	0,68	0,96	0,02	0,88	0,96
si_067	CD25	14,37	0,03	0,67	0,96	0,02	0,83	0,96
si_069	CD27	13,47	0,09	0,42	0,94	-0,06	0,68	0,96
si_070	CD28	15,46	0,26	0,19	0,94	0,07	0,76	0,96
si_071	CD29	13,27	-0,01	0,86	0,99	0,00	0,96	0,99
si_072	CD29	13,22	-0,09	0,46	0,95	-0,20	0,18	0,96
si_073	CD30	13,27	0,10	0,13	0,94	0,04	0,60	0,96
si_074	CD31	13,77	-0,02	0,79	0,99	0,09	0,38	0,96
si_075	CD33	13,76	0,03	0,62	0,96	0,01	0,90	0,97
si_076	CD34	13,59	0,04	0,60	0,96	0,08	0,39	0,96
si_077	CD36	13,14	-0,13	0,30	0,94	0,06	0,71	0,96
si_078	CD37	13,50	-0,10	0,42	0,94	0,12	0,42	0,96
si_079	CD38	13,62	-0,07	0,68	0,96	0,09	0,66	0,96
si_080	CD40	14,52	-0,07	0,64	0,96	0,06	0,76	0,96
si_081	CD41	13,47	0,07	0,25	0,94	-0,02	0,77	0,96
si_082	CD41a	14,04	0,02	0,70	0,96	-0,06	0,40	0,96
si_083	CD42b	13,67	0,09	0,28	0,94	0,06	0,54	0,96
si_084	CD43	14,52	-0,04	0,63	0,96	-0,03	0,73	0,96
si_085	CD43	13,63	0,05	0,60	0,96	-0,09	0,37	0,96
si_086	CD44	14,17	0,21	0,01	0,49	0,13	0,12	0,94
si_087	CD44	14,25	0,14	0,12	0,94	0,08	0,45	0,96
si_088	CD45	15,07	0,06	0,38	0,94	0,03	0,70	0,96
si_090	CD45	15,34	-0,01	0,85	0,99	0,03	0,74	0,96
si_091	CD45RA	15,72	0,02	0,88	0,99	0,03	0,83	0,96

si_092	CD45RA	13,65	-0,09	0,32	0,94	0,05	0,61	0,96
si_093	CD45RA	14,29	0,06	0,50	0,96	0,06	0,62	0,96
si_094	CD45RB	15,87	-0,03	0,57	0,96	-0,10	0,17	0,96
si_095	CD45RO	11,89	-0,19	0,16	0,94	-0,13	0,42	0,96
si_096	CD46	14,79	-0,14	0,24	0,94	-0,21	0,17	0,96
si_097	CD47	13,55	0,04	0,63	0,96	-0,03	0,70	0,96
si_098	CD47	13,68	0,00	1,00	1,00	0,04	0,76	0,96
si_099	CD48	13,21	0,00	0,98	1,00	0,04	0,67	0,96
si_100	CD50	13,33	0,05	0,68	0,96	0,08	0,55	0,96
si_101	CD52	13,10	0,13	0,06	0,93	0,02	0,83	0,96
si_102	CD53	13,38	-0,13	0,21	0,94	-0,21	0,07	0,94
si_103	CD53	14,31	0,42	0,00	0,12	0,36	0,01	0,70
si_104	CD54	13,25	-0,14	0,25	0,94	-0,28	0,05	0,94
si_105	CD54	14,41	0,33	0,01	0,52	0,37	0,02	0,75
si_106	CD55	13,32	0,01	0,89	0,99	-0,01	0,92	0,98
si_107	CD55	13,41	0,13	0,15	0,94	0,07	0,51	0,96
si_108	CD56	13,48	-0,10	0,32	0,94	-0,11	0,32	0,96
si_109	CD56	14,70	-0,11	0,27	0,94	0,03	0,81	0,96
si_110	CD57	13,39	-0,18	0,31	0,94	0,03	0,90	0,97
si_111	CD58	15,49	-0,05	0,74	0,97	0,05	0,75	0,96
si_112	CD58	13,75	-0,04	0,69	0,96	0,05	0,62	0,96
si_113	CD59	13,82	-0,08	0,50	0,96	-0,21	0,11	0,94
si_114	CD59	14,79	0,04	0,68	0,96	-0,03	0,78	0,96
si_115	CD62L	14,05	0,05	0,57	0,96	0,05	0,62	0,96
si_116	CD62L	13,11	0,19	0,06	0,93	0,25	0,04	0,94
si_117	CD62p	13,17	0,21	0,02	0,52	0,06	0,58	0,96
si_118	CD63	13,95	0,05	0,51	0,96	0,02	0,84	0,96
si_119	CD66e	13,63	-0,16	0,15	0,94	-0,29	0,03	0,94
si_120	CD69	13,71	0,13	0,13	0,94	-0,06	0,53	0,96

si_121	CD71	13,24	0,06	0,44	0,94	0,00	0,98	0,99
si_122	CD71	13,51	0,08	0,35	0,94	0,13	0,23	0,96
si_123	CD72	13,54	0,11	0,12	0,94	0,13	0,11	0,94
si_124	CD72	14,01	-0,17	0,27	0,94	-0,07	0,70	0,96
si_125	CD79a	14,22	-0,14	0,15	0,94	0,07	0,52	0,96
si_126	CD80	13,43	-0,04	0,80	0,99	0,12	0,55	0,96
si_127	CD86	13,39	-0,22	0,08	0,94	0,02	0,88	0,96
si_128	CD95	15,54	0,12	0,45	0,95	0,27	0,17	0,96
si_129	CD97	14,83	0,00	0,98	1,00	-0,14	0,20	0,96
si_130	CD98	13,49	0,22	0,02	0,57	0,15	0,18	0,96
si_131	CD99	14,36	0,00	0,97	1,00	0,08	0,52	0,96
si_132	CD99R	13,53	-0,09	0,35	0,94	0,16	0,14	0,96
si_133	CD105	13,64	0,09	0,36	0,94	-0,05	0,65	0,96
si_134	CD105	13,85	-0,05	0,62	0,96	-0,21	0,08	0,94
si_135	CD106	13,80	0,02	0,77	0,99	0,10	0,27	0,96
si_136	CD147	14,07	0,05	0,50	0,96	-0,15	0,10	0,94
si_137	CD147	13,72	0,07	0,36	0,94	0,10	0,26	0,96
si_138	CD162	14,81	0,08	0,56	0,96	0,18	0,26	0,96
si_139	CD177	12,81	-0,01	0,84	0,99	-0,06	0,45	0,96
si_140	CD222	13,58	0,01	0,89	0,99	-0,04	0,72	0,96
si_141	CD235a	13,78	-0,11	0,46	0,95	0,13	0,46	0,96
si_142	CD235a b	15,10	0,15	0,30	0,94	0,30	0,08	0,94
si_143	HLA-ABC	14,93	0,01	0,92	0,99	-0,06	0,59	0,96
si_144	HLA-DR	13,65	-0,05	0,66	0,96	0,04	0,79	0,96
si_145	HLA-DP	13,92	0,05	0,54	0,96	0,04	0,71	0,96
si_146	pan HLA-class II	11,51	0,06	0,46	0,95	0,07	0,49	0,96
si_147	IL-6	13,71	0,07	0,28	0,94	0,07	0,35	0,96
si_148	TSLPrec	12,58	-0,28	0,05	0,86	-0,03	0,86	0,96

si_149	CD13	15,36	0,11	0,20	0,94	0,15	0,14	0,96
si_151	HLA I	13,31	0,07	0,31	0,94	0,01	0,93	0,98
si_152	ANCA	12,99	-0,11	0,28	0,94	-0,17	0,17	0,96
si_153	BDNF	12,70	-0,12	0,30	0,94	-0,08	0,58	0,96
si_154	Eotoxin-1	13,48	-0,08	0,64	0,96	-0,01	0,95	0,99
si_155	FDC	11,79	0,00	0,98	1,00	-0,12	0,19	0,96
si_156	GM-CSF	13,56	0,02	0,82	0,99	0,02	0,84	0,96
si_157	IFN gamma	13,46	-0,09	0,41	0,94	0,08	0,51	0,96
si_158	IgE	14,07	-0,01	0,91	0,99	0,04	0,79	0,96
si_159	IL-1 beta	12,87	-0,37	0,02	0,57	-0,10	0,58	0,96
si_160	IL-7	12,87	-0,26	0,16	0,94	-0,02	0,93	0,98
si_161	IL-8	13,16	-0,19	0,01	0,52	-0,16	0,07	0,94
si_162	IL-10	13,47	-0,06	0,64	0,96	-0,13	0,40	0,96
si_163	IL-15	13,01	-0,22	0,09	0,94	-0,09	0,55	0,96
si_164	IL-18	13,12	-0,16	0,32	0,94	0,00	0,99	0,99
si_165	MIP-1alpha	12,93	-0,06	0,61	0,96	-0,05	0,69	0,96
si_166	MCP-3	13,22	-0,13	0,21	0,94	-0,11	0,37	0,96
si_167	MPO	13,22	0,04	0,62	0,96	-0,10	0,31	0,96
si_168	NTAL	13,04	0,04	0,73	0,97	0,08	0,54	0,96
si_169	NT-4	14,00	-0,20	0,21	0,94	-0,02	0,90	0,97
si_170	p53	13,69	-0,03	0,67	0,96	-0,09	0,33	0,96
si_171	p72Syk	13,34	0,09	0,13	0,94	0,09	0,19	0,96
si_172	TSLPR	12,51	-0,20	0,11	0,94	-0,03	0,83	0,96
si_173	CD79a	15,05	-0,16	0,09	0,94	-0,11	0,33	0,96
si_174	IFNalpha	13,37	-0,41	0,01	0,49	-0,13	0,45	0,96
si_175	Cox1	12,01	-0,22	0,12	0,94	-0,19	0,25	0,96
si_177	tTG	12,26	-0,09	0,71	0,96	-0,14	0,62	0,96
si_180	CD3	14,39	0,11	0,33	0,94	-0,06	0,63	0,96

si_182	CD4	12,88	-0,08	0,41	0,94	-0,18	0,13	0,96
si_183	CD4	13,89	0,00	0,96	1,00	-0,10	0,19	0,96
si_184	CD4	14,76	-0,05	0,58	0,96	-0,17	0,14	0,96
si_185	CD4	13,13	-0,06	0,39	0,94	-0,08	0,32	0,96
si_186	CD5	13,99	0,01	0,95	0,99	-0,11	0,28	0,96
si_187	CD8	13,29	-0,07	0,34	0,94	-0,08	0,34	0,96
si_188	CD9	12,16	0,01	0,88	0,99	0,05	0,59	0,96
si_189	CD16	14,59	-0,11	0,34	0,94	0,05	0,76	0,96
si_190	CD21	14,51	-0,13	0,14	0,94	-0,12	0,24	0,96
si_191	CD29	13,57	-0,13	0,38	0,94	-0,20	0,26	0,96
si_192	CD31	13,74	-0,04	0,75	0,98	0,01	0,97	0,99
si_193	CD35	13,39	0,05	0,62	0,96	-0,04	0,71	0,96
si_194	CD38	13,44	0,03	0,65	0,96	0,03	0,75	0,96
si_195	CD41	13,17	0,08	0,26	0,94	0,05	0,51	0,96
si_196	CD41	13,28	-0,02	0,89	0,99	0,08	0,63	0,96
si_197	CD41b	11,99	0,15	0,17	0,94	-0,13	0,33	0,96
si_198	CD44	15,66	0,01	0,94	0,99	0,11	0,40	0,96
si_199	CD44	15,41	0,09	0,29	0,94	0,06	0,54	0,96
si_200	CD47	14,52	0,11	0,15	0,94	-0,03	0,77	0,96
si_201	CD49d	12,97	0,01	0,91	0,99	0,01	0,94	0,98
si_202	CD53	13,07	0,01	0,89	0,99	0,06	0,46	0,96
si_203	CD55	13,58	0,11	0,16	0,94	0,03	0,73	0,96
si_204	CD61	14,21	-0,04	0,61	0,96	0,08	0,39	0,96
si_206	CD63	13,76	-0,08	0,45	0,94	-0,01	0,92	0,98
si_208	CD71	12,96	0,07	0,69	0,96	0,14	0,49	0,96
si_209	CD98	13,07	0,07	0,57	0,96	0,07	0,66	0,96
si_210	CD106	14,47	0,09	0,39	0,94	0,04	0,76	0,96
si_211	CD116	11,22	-0,01	0,92	0,99	-0,02	0,76	0,96
si_212	CD123	13,58	0,01	0,91	0,99	0,12	0,30	0,96
si_213	CDw131	12,93	0,07	0,44	0,94	-0,08	0,49	0,96
si_214	CD139	12,78	-0,30	0,01	0,52	-0,22	0,10	0,94

si_215	HLA-I	13,92	0,03	0,70	0,96	-0,04	0,67	0,96
si_217	IFNg	12,96	-0,03	0,65	0,96	0,02	0,82	0,96
si_218	IFNg	13,97	-0,05	0,49	0,96	-0,02	0,78	0,96
sj_001	HCD137	14,10	-0,10	0,40	0,94	0,04	0,77	0,96
sj_018	IL-37	14,07	-0,08	0,42	0,94	0,02	0,87	0,96
sj_019	IL-37	13,53	0,21	0,09	0,94	0,33	0,03	0,94
sj_030	IL-8	13,11	-0,07	0,53	0,96	-0,05	0,71	0,96
sj_031	IL-8	12,69	-0,02	0,86	0,99	0,02	0,82	0,96
sj_032	IL-8	11,30	-0,01	0,91	0,99	0,06	0,60	0,96
sj_044	IFNy	12,84	0,06	0,42	0,94	0,05	0,54	0,96
sj_045	IFNy	12,05	0,12	0,22	0,94	0,14	0,19	0,96
sj_046	IFNy	11,46	0,21	0,18	0,94	0,00	0,99	0,99
sj_049	TNFa	13,23	0,06	0,55	0,96	-0,04	0,72	0,96
sj_050	TNFa	13,24	0,04	0,56	0,96	0,04	0,63	0,96
sj_051	TNFa	13,20	0,00	0,97	1,00	-0,09	0,46	0,96
sj_062	IL-10	13,21	0,03	0,64	0,96	0,04	0,63	0,96
sj_063	IL-10	13,99	-0,03	0,66	0,96	0,10	0,25	0,96
sj_064	IL-10	13,46	0,05	0,43	0,94	0,06	0,36	0,96
sj_066	IL-4	14,04	-0,05	0,61	0,96	-0,21	0,08	0,94
sj_067	IL-4	13,36	-0,13	0,37	0,94	0,11	0,54	0,96
sj_068	IL-4	13,18	-0,22	0,21	0,94	-0,01	0,98	0,99
sj_079	TSLP	14,15	-0,01	0,95	0,99	0,05	0,80	0,96
sj_080	TSLP	13,28	-0,04	0,74	0,97	0,06	0,71	0,96
sj_084	TRAIL	14,41	-0,05	0,80	0,99	0,11	0,61	0,96
sj_085	TRAIL	12,83	0,03	0,71	0,96	-0,02	0,86	0,96
sj_090	IL-12B	15,87	-0,07	0,17	0,94	-0,12	0,04	0,94
sj_091	IL-12B	13,55	0,18	0,14	0,94	0,20	0,16	0,96
sj_246	CEACAM1	13,72	-0,02	0,81	0,99	-0,10	0,33	0,96
sj_247	CEACAM3	13,39	-0,12	0,21	0,94	-0,27	0,02	0,75
sj_248	CEACAM5	14,51	-0,09	0,27	0,94	-0,20	0,04	0,94

sj_249	CEACAM6	14,00	0,00	1,00	1,00	-0,04	0,82	0,96
sj_250	CEACAM8	14,02	0,00	0,98	1,00	-0,17	0,40	0,96
sj_251	CEACAM1	14,29	-0,13	0,37	0,94	-0,11	0,52	0,96
sj_270	CYTL	12,03	0,10	0,32	0,94	0,08	0,53	0,96
sj_271	CYTL	12,91	-0,03	0,74	0,97	0,00	0,99	0,99
sj_272	RANTES	12,84	-0,21	0,18	0,94	-0,09	0,64	0,96
sj_273	RANTES	12,57	-0,18	0,31	0,94	0,03	0,87	0,96
sj_295	IL-13	13,58	-0,08	0,36	0,94	-0,20	0,07	0,94
sj_302	IL-12p70	13,54	-0,15	0,19	0,94	0,02	0,87	0,96
sj_311	MIP-4	15,71	0,00	0,98	1,00	-0,05	0,71	0,96
sj_320	IL-1beta	12,67	0,19	0,02	0,52	0,08	0,41	0,96
sj_324	IL-1alpha	12,92	-0,16	0,40	0,94	-0,07	0,76	0,96
sj_325	IL-1alpha	13,03	0,07	0,65	0,96	0,07	0,71	0,96
sj_328	MCP-2	13,28	-0,01	0,88	0,99	-0,11	0,15	0,96
sj_329	MCP-2	12,63	-0,12	0,16	0,94	-0,15	0,12	0,94
sj_333	MCP-3	13,37	-0,18	0,04	0,73	-0,29	0,00	0,59
sj_334	MCP-3	13,22	0,01	0,87	0,99	0,02	0,87	0,96
sj_339	IL-16	13,05	-0,12	0,48	0,96	0,06	0,74	0,96
sj_342	IL-6	12,48	-0,13	0,15	0,94	-0,07	0,52	0,96
sj_343	LIF	14,64	-0,21	0,31	0,94	0,07	0,77	0,96

[a]The antibody ID used for protein detection. In the analysis, many proteins were evaluated using several antibodies, targeted at different epitopes. [b]Average protein expression (normalized Log2 signal from the microarray readout). [c]Log2 fold change between fatigue/non-fatigue and cognitive dysfunction/non-cognitive dysfunction. LogFc = 1 means that the concentration in the fatigue group is 2^1 = 2 times higher compared to the control group. [d]P-value for the difference between the groups. [e]P-value adjusted with the Benjamini-Hochberg method.

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