**Supplemental Digital Content 1**

**List of the 92 proteins analyzed in the multiplex proximity extension assay (PEA)**

For extensive background information on the method, see <http://www.olink.com/wp-content/uploads/2015/12/0993-v1.1-Proseek-Multiplex-Inflammation-I-Data-Package_final.pdf> (retrieved 4 July 2017).

|  |  |  |
| --- | --- | --- |
| Long name (short name) | UniProt No. | LOD (pg/mL) |
| Adenosine Deaminase (ADA) | P00813 | 0.48 |
| Artemin (ARTN) | Q5T4W7 | 0.24 |
| Axin-1 (AXIN1) | O15169 | 61,0 |
| Beta-nerve growth factor (Beta-NGF) | P01138 | 0.48 |
| Brain-derived neutrophic factor (BDNF) | P23560 |   |
| Caspase 8 (CASP-8) | Q14790 | 0.48 |
| C-C motif chemokine 4 (CCL4) | P13236 | 1.9 |
| C-C motif chemokine 19 (CCL19) | Q99731 | 15,0 |
| C-C motif chemokine 20 (CCL20) | P78556 | 7.6 |
| C-C motif chemokine 23 (CCL23) | P55773 | 31,0 |
| C-C motif chemokine 25 (CCL25) | O15444 | 3.8 |
| C-C motif chemokine 28 (CCL28) | Q9NRJ3 | 61,0 |
| CD40L receptor (CD40) | P25942 | 0.01 |
| CUB domain-containing protein 1 (CDCP1) | Q9H5V8 | 0.12 |
| C-X-C motif chemokine 1 (CXCL1) | P09341 | 3.8 |
| C-X-C motif chemokine 5 (CXCL5) | P42830 | 0.95 |
| C-X-C motif chemokine 6 (CXCL6) | P80162 | 7.6 |
| C-X-C motif chemokine 9 (CXCL9) | Q07325 | 0.95 |
| C-X-C motif chemokine 10 (CXCL10) | P02778 | 7.6 |
| C-X-C motif chemokine 11 (CXCL11) | O14625 | 7.6 |
| Cystatin D (CST5) | P28325 | 1.9 |
| Delta and Notch-like epidermal growth factor related receptor (DNER) | Q8NFT8 | 0.95 |
| Eotaxin-1 (CCL11) | P51671 | 3.8 |
| Eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) | Q13541 |   |
| Fibroblast growth factor 5 (FGF-5) | Q8NF90 | 1.9 |
| Fibroblast growth factor 19 (FGF-19) | O95750 | 7.6 |
| Fibroblast growth factor 21 (FGF-21) | Q9NSA1 | 31,0 |
| Fibroblast growth factor 23 (FGF-23) | Q9GZV9 | 122,0 |
| Fms-related tyrosine kinase 3 ligand (FIt3L) | P49771 | 0.01 |
| Fractalkine (CX3CL1) | P78423 | 15.3 |
| Glial cell line-derived neutrophic factor (hGDNF) | P39905 | 0.01 |
| Hepatocyte growth factor (HGF) | P14210 | 7.6 |
| Interferon gamma (IFN-gamma) | P01579 | 15.3 |
| Interleukin-1 alpha (IL-1 alpha) | P01583 | 0.48 |
| Interleukin-2 (IL-2) | P60568 | 30.5 |
| Interleukin-2 receptor subunit beta (IL-2RB) | P14784 | 15,0 |
| Interleukin-4 (IL-4) | P05112 | 0.24 |
| Interleukin-5 (IL-5) | P05113 | 3.8 |
| Interleukin-6 (IL-6) | P05231 | 0.12 |
| Interleukin-7 (IL-7) | P13232 | 0.24 |
| Interleukin-8 (IL-8) | P10145 | 0.03 |
| Interleukin-10 (IL-10) | P22301 | 0.48 |
| Interleukin-10 receptor subunit alpha (IL-10RA) | Q13651 | 3.8 |
| Interleukin-10 receptor subunit beta (IL10RB) | Q08334 | 0.12 |
| Interleukin-12 subunit beta (IL-12B) | P29460 | 0.12 |
| Interleukin-13 (IL-13) | P35225 | 7.6 |
| Interleukin-15 receptor subunit alpha (IL-15RA) | Q13261 | 0.95 |
| Interleukin-17A (IL-17A) | Q16552 | 3.8 |
| Interleukin-17C (IL-17C) | Q9P0M4 | 31,0 |
| Interleukin-18 (IL-18) | Q14116 | 0.06 |
| Interleukin-18 receptor 1 (IL-18R1) | Q13478 | 0.06 |
| Interleukin-20 (IL-20) | Q9NYY1 | 7.6 |
| Interleukin-20 receptor subunit alpha (IL-2oRA) | Q9UHF4 | 1.9 |
| Interleukin-22 receptor subunit alpha-1 (IL-22RA1) | Q8N6P7 | 0.24 |
| Interleukin-24 (IL-24) | Q13007 | 1.9 |
| Interleukin-33 (IL-33) | O95760 | 3.8 |
| Latency-associated peptide transforming growth factor beta 1 (LAP TGF-beta-1) | P01137 | 61 |
| Leukemia inhibitory factor (LIF) | P15018 | 3.8 |
| Leukemia inhibitory factor receptor (LIF-R) | P42702 | 30.5 |
| Macrophage colony-stimulating factor 1 (CSF-1) | P09603 | 0.004 |
| Macrophage inflammatory protein 1-alpha (MIP-1 alpha) | P10147 | 0.06 |
| Matrix metalloproteinase-1 (MMP-1) | P03956 | 1.9 |
| Matrix metalloproteinase-10 (MMP-10) | P09238 | 0.95 |
| Monocyte chemotactic protein 1 (MCP-1) | P13500 | 0.03 |
| Monocyte chemotactic protein 2 (MCP-2) | P80075 | 0.06 |
| Monocyte chemotactic protein 3 (MCP-3) | P80098 | 0.48 |
| Monocyte chemotactic protein 4 (MCP-4) | Q99616 | 7.6 |
| Natural killer cell receptor 2B4 (CD244) | Q9BZW8 | 0.06 |
| Neurotrophin-3 (NT-3) | P20783 | 0.12 |
| Neurturin (NRTN) | Q99748 | 3.8 |
| Oncostatin-M (OSM) | P13725 | 0.03 |
| Osteoprotegerin (OPG) | O00300 | 0.24 |
| Programmed cell death 1 ligand 1 (PD-L1) | Q9NZQ7 | 3.8 |
| Protein S100-A12 (EN-RAGE) | P80511 | 122 |
| Signaling lymphocytic activation molecule (SLAMF1) | Q13291 | 31,0 |
| SIR2-like protein 2 (SIRT2) | Q8IXJ6 | 7.6 |
| STAM-binding protein (STAMBP) | O95630 | 7.6 |
| Stem cell factor (SCF) | P21583 | 1.9 |
| Sulfotransferase 1A1 (ST1A1) | P50225 | 244 |
| T-cell surface glycoprotein CD5 (CD5) | P06127 | 0.06 |
| T-cell surface glycoprotein CD6 isoform (CD6) | Q8WWJ7 | 0.24 |
| Thymic stromal lymphopoietin (TSLP) | Q969D9 | 3.8 |
| TNF-beta (TNFB) | P01374 | 0.24 |
| TNF-related activation cytokine (TRANCE) | O14788 | 3.8 |
| TNF-related apoptosis ligand (TRAIL) | P50591 | 0.95 |
| Transforming growth factor alpha (TGF-alpha) | P01135 | 0.48 |
| Tumor necrosis factor (Ligand) superfamily member 12 (TWEAK) | Q4ACW9 | 1.9 |
| Tumor necrosis factor (TNF) | P01375 | 0.48 |
| Tumor necrosis factor ligand superfamily member 14 (TNFSF14) | O43557 | 0.95 |
| Tumor necrosis factor receptor superfamily member 9 (TNFRSF9) | Q07011 | 0.03 |
| Urokinase-type plasminogen activator (uPA) | P00749 | 0.12 |
| Vascular endothelial growth factor A (VEGF\_A) | P15692 | 0.06 |

\*Limit of detection (LoD) defined as 3 standard deviations above background

**Supplemental Digital Content 1, continued**

**Method validation for plasma CXCL1 and CXCL10**

In another cohort of treatment-refractory chronic pain patients, we have correlated results from the present PEA panel to results from an electrochemiluminescence immunoassay (Meso Scale Discovery MULTI-ARRAY® technology, <https://www.mesoscale.com/>). The Pearson correlation coefficient was 0.94 for CXCL10 (n=52, p<0.001) and 0.76 for CXCL1 (n=56, p<0.001). The plots are as follows:





**Legend:**

**NPXlin**= linearized Normalized Protein eXpression (NPX), i.e., PEA results.

**MSD**=concentration according to the Meso Scale Discovery Assay (pg/ml)

**Supplemental Digital Content 1, continued**

**Intraassay coefficients of variations (CV) for the major findings of the study, including CXCL1**

The following data were provided by the manufacturer, <http://www.olink.com/wp-content/uploads/2015/12/0993-v1.1-Proseek-Multiplex-Inflammation-I-Data-Package_final.pdf> (retrieved 4 July 2017). Hence, the within series CVs for the following analytes range 5-8% with a volume of 1 ul (the CV is the combination of the pipetting CV and the CV of the actual assay).

|  |  |
| --- | --- |
|  | Intra-assaycoefficient of variation |
| CXCL1 | 6% |
| CXCL6 | 8% |
| CXCL10 | 7% |
| CCL8 | 6% |
| CCL11 | 5% |
| CCL23 | 6% |
| LAPTGF-beta-1 | 7% |

**Supplemental Digital Content 2**

**Statistical considerations**

In the present study, we examined 92 proteins. When analyzing many variables, the so-called multiple testing problem is an ever-present concern [37]. Theoretically, using a traditional significance level of 0.05, if “k” is the number of comparisons, the risk of a least one false positive is 1-0.95k [11]. So when for instance 90 variables are examined, the risk of at least one false positive finding would hence be 99%. However, the formula assumes that the variables are *independent* of each other, and when looking at cytokines and chemokines, this assumption is not well-founded. Moreover, controlling the family wise error rate by a Bonferroni correction tends to be far too conservative, leading to low power. Instead, for our main comparison between cohorts 1a and 1b, we controlled the false discovery rate (FDR) using the procedure of Benjamini and Hochberg [2]. Given a FDR of 0.1, up to 1/10 of findings are likely to be false positives. Importantly, no biomarker candidate was down-regulated. Hence, although a few false positive markers may be present, we think that it does not seem sensible to dismiss our results as a gigantic type I error. The possibility of medication and/or co-morbidities being a confounding factor should however be acknowledged.

As a complement to FDR and confirmation, we also used orthogonal partial least squares – discriminant analysis (OPLS-DA). OPLS-DA includes all variables simultaneously, taking the correlation structure of the data set into consideration, thereby favouring structure and information over “noise” [11]. The method used in the present paper is the same as used by our group in a number of recent peer-reviewed publications [3-6; 13; 14; 16; 30; 31] and it is congruent with the principles argued for by Wheelock & Wheelock [40]. Classical statistical methods such as multiple linear regression (MLR) and logistic regression (LR) can quantify the level of relations of individual factors but disregard interrelationships among different factors and thereby ignore system-wide aspects (e.g., when a group of variables correlates with the investigated dependent outcome) [19]. Classical methods assume variable independence when interpreting results [34] and there are several risks considering one variable at a time [11]. MLR and LR assume that the regressor (X) variables are independent. If multicollinearity (i.e., high correlations) occurs among the X-variables, the regression coefficients become unstable and their interpretabilitybreaks down. Moreover, such methods also assume that a high subject-to-variables ratio is present (e.g., >5) and such requirements are not required for OPLS-DA; in fact, OPLS-DA can handle subject-to-variables ratios < 1. Remarkably, the 11 proteins found by OPLS-DA when comparing cohorts 1a and 1b were exactly the same as the proteins found my multiple univariate testing with control of FDR. All in all, we think that although the multiple testing issue should not be dismissed too lightly, it should not on the other hand be exaggerated.

Finally, and as an example, one can for instance see in **Table 2** that the increase is largest for CCL19 (91%) but, according to the OPLS-DA regression, proteins with a higher VIP than CCL19 (i.e. >1.5) are nevertheless more important than CCL19 for group discrimination. This is due to the fact that OPLS-DA weighs in all the variables simultaneously, not one by one.

**Supplemental Digital Content 3**

**Chemokines**

Five of the six markers significantly associated with NeuP in both cohorts were chemokines. The chemokine family consists of approximately 50 basic proteins with a molecular weight of approximately 8-15 kDa. They are expressed by a wide range of normal and tumour cells [22; 23; 33]. Chemokines have a molecular structure containing four NH2-terminal cysteine residues and are divided into four subfamilies depending on their structure [22; 23; 33]: CXC chemokines, CC chemokines, C chemokines, and CX3C chemokines. In this study, we found two members of the CXC subfamily (CXCL6, CXCL10) and three members of the CC subfamily (CCL8, CCL11, CCL23) significantly associated with NeuP in both cohorts.

In addition to the referenced information given in the “Chemokines and neuroinflammation” subsection of the discussion, the following is also noteworthy. Nerve injury increases spinal cord production of neuronal CXCL13, which can interact with the CCR5 receptor on astrocytes to maintain neuropathic pain-behavior in mice [20]. Neutralizing the action of chemokines CCL2 or CX3CL1 attenuates nerve-injury induced pain-like behavior in rodents [9; 12; 27; 28; 38; 41]. Concerning CCL11, this chemokine was previously investigated in at least the following three models of neuropathic pain. CCL11 was found to be upregulated in the spinal cord in an animal model of chemotherapy-induced neuropathic pain [25], but remained undetectable in the spinal cord dorsal horn and dorsal root ganglion after chronic constriction of the sciatic nerve [21]. The antinociceptive benefit of mice with altered T cell immune response has been suggested to include reduced spinal cord levels of CCL11 [36].

**LAPTGF-beta-1**

The sixth CSF marker associated with NeuP in both cohorts was LAPTGF-beta-1. Remarkably, LAPTGF-beta-1 has been associated with chronic pain conditions in a number of recent studies using the same PEA panel, both in CSF and plasma/serum [6; 13; 29]. LAPTGF-beta-1 is the latency-associated peptide complex of TGF-beta-1. Intrathecal infusion of TGF-beta-1 was recently reported to suppress the nerve injury-induced inflammatory response (cytokine expression) and glial activation in the spinal cord [10] and has been shown to inhibit neuropathic pain-like behavior in a murine chronic constriction model of neuropathic pain [8]. TGF-beta latency-associated peptides can block the TGF-beta-1-mediated breakdown of endothelial barriers [1]. An experimental cell culture study showed that exposure to proinflammatory conditions (LPS and interferon-gamma) increased the LAPTGF-beta-1 and TGF-beta-1 activity in hippocampal neurons [17]. Perhaps the high CSF levels of LAPTGF-beta1 we detected in NeuP patients mirror a response to high proinflammation and, in fact, is part of an elevated but insufficient anti-nociceptive mechanism in chronic pain patients.

**“Classical” cytokines and neurotrophic factors**

The process of gliosis is thought to be characterized among other things by activated microglia releasing key multifunctional cytokines (TNF-α, IL-6) that initiate and orchestrate the subsequent production of downstream cytokines and other pro-algesic mediators [15; 26; 39]. In the context of the present study, and focusing on the more reliable comparison between cohorts 1a and 1b (more reliable because samples were collected at the same centre), it is therefore important to report that levels of TNF-α were below LoD, and that levels of IL-6 did not differ between groups. Another classical cytokine for pain regulation, IL-1b, was not part of the present panel.

Given previous studies [7; 24], it is also important to report some key negative findings concerning some classical neurotrophic factors that are part of the present panel of inflammation-related proteins: neither BDNF, GDNF, nor beta-NGF were significant. However, this was for different reasons. Levels of BDNF were measurable but did not differ at all between groups. Levels of GDNF were under LoD. Beta-NGF was detectable and had a low VIP (0.91), indicating below-average influence on class separation; however, when looking specifically at beta-NGF using traditional univariate statistics, a statistically significant difference was found (p=0.047), with beta-NGF being up-regulated in patients. Hence, although beta-NGF was far from being part of the most important proteins for class discrimination when looking at the total correlation structure of the material, it still was significant by traditional univariate statistics. Whether this indicates that beta-NGF is a false positive finding or not, is difficult to say.

**CSF vs systemic levels**

The CSF is arguably an important potential “mirror” for pathophysiological processes in the spinal cord [3; 35]. Because of the blood-CSF barrier (BCB) and the blood-brain barrier (BBB), it is incorrect to view the CSF as merely an ultrafiltrate of plasma and, in general, proteins found at levels much greater than 0.5% of plasma concentrations probably undergo some local synthesis within the CNS [18]. CSF cytokines may come from glial cells (e.g., microglia) or from the few infiltrating leukocytes present in the meninges or the subarachnoid space [18] (microglia are the specialized phagocytes of the CNS [32], but they also have a number of other key roles in addition of their function as immune surveyors, e.g., synaptic pruning, maturation of established synapses, and maintenance of synaptic plasticity [32]). The present study lacks information on peripheral levels of cytokines, but in a previous study involving five cytokines, CSF levels were far greater than 0.5% of blood levels; for instance, the CSF/blood ratio of mean values was 366% for IL-8, and 28% for TNF-α [24]. Hence, it is not unreasonable to assume that the present findings might mirror inflammatory activity in the CNS rather than mirroring plasma levels. Future studies relating the inflammatory fingerprints of CSF and blood to each with the same controls for both biofluids will probably cast more light on this issue.

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