

Supplementary file

Supplementary Table I. Overview of the 85 inflammatory proteins measured on the custom Luminex® multiplex assay.

#	Name protein	#	Name protein	#	Name protein	#	Name protein	#	Name protein
1.	Adiponectin	21.	CXCL5 ¹⁹	41.	IL-3	61.	IL-29	81.	TNF-R2
2.	Adipsin	22.	CXCL9 ²⁰	42.	IL-4	62.	IL-33	82.	TPO ⁴⁷
3.	Cathepsin B ¹	23.	CXCL10 ²¹	43.	IL-5	63.	LAIR-1 ³¹	83.	TSLP
4.	Cathepsin L ²	24.	CXCL13 ²²	44.	IL-6	64.	Leptin ³²	84.	V-CAM ⁴⁸
5.	Cathepsin S ³	25.	CD14	45.	IL-7	65.	LIGHT ³³	85.	VEGF
6.	CCL1 ⁴	26.	CD121a ²³	46.	IL-8	66.	M-CSF ³⁴		
7.	CCL2 ⁵	27.	CD121b ²⁴	47.	IL-9	67.	MIF ³⁵		
8.	CCL3 ⁶	28.	FGF basic ²⁵	48.	IL-10	68.	MMP-8 ³⁶		
9.	CCL4 ⁷	29.	G-CSF ²⁶	49.	IL-11	69.	NGF ³⁷		
10.	CCL5 ⁸	30.	GM-CSF ²⁷	50.	IL-12	70.	OPG ³⁸		
11.	CCL7 ⁹	31.	HGF ²⁸	51.	IL-13	71.	OPN ³⁹		
12.	CCL11 ¹⁰	32.	I-CAM1 ²⁹	52.	IL-15	72.	PAI-1 ⁴⁰		
13.	CCL17 ¹¹	33.	IFN- α	53.	IL-16	73.	PD-1 ⁴¹		
14.	CCL18 ¹²	34.	IFN- β	54.	IL-17	74.	RBP4 ⁴²		
15.	CCL19 ¹³	35.	IFN- γ	55.	IL-18	75.	Resistin ⁴³		
16.	CCL20 ¹⁴	36.	IL-1RA	56.	IL-21	76.	SAA-1 ⁴⁴		
17.	CCL22 ¹⁵	37.	IL-1 α	57.	IL-22	77.	TIMP-1 ⁴⁵		
18.	CCL27 ¹⁶	38.	IL-1 β	58.	IL-23	78.	TNF- α		
19.	Chemerin ¹⁷	39.	IL-2	59.	IL-25	79.	TNF- β		
20.	CXCL4 ¹⁸	40.	IL-2R α ³⁰	60.	IL-27	80.	TNF-R1 ⁴⁶		

¹synonym: CTSB; ²synonym: CTSL; ³synonym: CTSS; ⁴synonym: I-309; ⁵synonym: MCP-1; ⁶synonym: MIP-1 α ; ⁷synonym: MIP-1 β ; ⁸synonym: RANTES; ⁹synonym: MCP-3; ¹⁰synonym: Eotaxin; ¹¹synonym: TARC; ¹²synonym: PARC; ¹³synonym: MIP-3 β ; ¹⁴synonym: MIP-3 α ; ¹⁵synonym: MDC; ¹⁶synonym: C-TACK; ¹⁷synonym: RARRES2; ¹⁸synonym: PF-4; ¹⁹synonym: ENA-78; ²⁰synonym: MIG; ²¹synonym: IP-10; ²²synonym: BLC; ²³synonym: IL-1R1; ²⁴synonym: IL-1R2; ²⁵synonym: FGF2; ²⁶synonym: CSF3G; ²⁷synonym: CSF2; ²⁸synonym: SF; ²⁹synonym: CD54; ³⁰synonym: CD25; ³¹synonym: CD305; ³²synonym: LEP; ³³synonym: TNFSF14; ³⁴synonym: CSF1; ³⁵synonym: GIF; ³⁶synonym: CLG1; ³⁷synonym: HSAN5; ³⁸synonym: TNFRSF11B; ³⁹synonym: BSP-1; ⁴⁰synonym: SERPINE1; ⁴¹synonym: CD279; ⁴²synonym: PRBP; ⁴³synonym: RETN; ⁴⁴synonym: PIG2; ⁴⁵synonym: EPA; ⁴⁶synonym: TNFRSF1A; ⁴⁷synonym: MSA; ⁴⁸synonym: CD106. Synonyms according to the National Center for Biotechnology Information (NCBI) Gene database.

Supplementary Table II. The top five significant GO terms with the highest observed gene count within the three strategy arms.

Pathway ID	Pathway description	Count	FDR
<i>Tocilizumab plus methotrexate</i>			
GO:0005615	Extracellular space	8	1.84 ^{E-06}
GO:0005576	Extracellular region	8	1.06 ^{E-02}
GO:0002684	Positive regulation of immune system process	6	1.36 ^{E-03}
GO:0051239	Regulation of multicellular organismal process	6	2.19 ^{E-02}
GO:0019221	Cytokine-mediated signalling pathway	5	1.36 ^{E-03}
<i>Tocilizumab</i>			
GO:0005615	Extracellular space	12	1.98 ^{E-10}
GO:0005576	Extracellular region	11	3.43 ^{E-03}
GO:0044421	Extracellular region part	10	5.38 ^{E-03}
GO:0006950	Response to stress	9	1.02 ^{E-02}
GO:0051246	Regulation of protein metabolic process	8	8.70 ^{E-03}
<i>Methotrexate</i>			
GO:0044699	Single-organism process	13	4.37 ^{E-03}
GO:0048522	Positive regulation of cellular process	12	2.07 ^{E-05}
GO:0044763	Single-organism cellular process	12	2.81 ^{E-02}
GO:0005615	Extracellular space	12	2.99 ^{E-11}
GO:0005576	Extracellular region	12	2.45 ^{E-05}

GO: gene ontology; FDR: false discovery rate.

Supplementary Table III. Overlapping significant GO terms found in the strategy arms between the proteomic and transcriptomics pathways*.

Pathway ID	Pathway description	FDR (protein)	FDR (mRNA)
<i>Tocilizumab</i>			
GO:0002687	Positive regulation of leukocyte migration	1.66 ^{E-02}	3.41 ^{E-02}
GO:0030595	Leukocyte chemotaxis	9.49 ^{E-03}	1.33 ^{E-03}
GO:0043065	Positive regulation of apoptotic process	3.35 ^{E-02}	4.41 ^{E-02}
GO:0051930	Regulation of sensory perception of pain	2.30 ^{E-02}	4.46 ^{E-02}
GO:0060326	Cell chemotaxis	3.00 ^{E-03}	2.93 ^{E-03}
<i>Methotrexate</i>			
GO:0048522	Positive regulation of cellular process	2.07 ^{E-05}	2.64 ^{E-02}
GO:0005615	Extracellular space	2.99 ^{E-11}	2.50 ^{E-03}
GO:0051704	Multi-organism process	1.88 ^{E-05}	1.10 ^{E-03}
GO:0010604	Positive regulation of macromolecule metabolic process	6.68 ^{E-06}	3.82 ^{E-02}
GO:0023051	Regulation of signalling	5.44 ^{E-05}	4.31 ^{E-02}
GO:0010646	Regulation of cell communication	7.07 ^{E-05}	2.06 ^{E-02}
GO:0050896	Response to stimulus	4.87 ^{E-02}	1.50 ^{E-02}
GO:0051707	Response to other organism	4.98 ^{E-08}	6.11 ^{E-07}
GO:0006955	Immune response	5.44 ^{E-05}	4.68 ^{E-02}
GO:0048584	Positive regulation of response to stimulus	5.44 ^{E-05}	3.50 ^{E-02}
GO:0002376	Immune system process	6.24 ^{E-05}	1.59 ^{E-02}
GO:0032268	Regulation of cellular protein metabolic process	1.47 ^{E-04}	4.98 ^{E-03}
GO:0009966	Regulation of signal transduction	2.18 ^{E-04}	4.21 ^{E-02}
GO:0080090	Regulation of primary metabolic process	7.82 ^{E-03}	1.85 ^{E-02}
GO:0001934	Positive regulation of protein phosphorylation	6.68 ^{E-06}	3.42 ^{E-02}
GO:0023056	Positive regulation of signalling	9.29 ^{E-05}	5.05 ^{E-03}
GO:0010647	Positive regulation of cell communication	1.55 ^{E-04}	5.44 ^{E-03}
GO:0009605	Response to external stimulus	4.83 ^{E-04}	6.12 ^{E-05}
GO:0010033	Response to organic stimulus	2.41 ^{E-03}	2.28 ^{E-03}
GO:0048583	Regulation of response to stimulus	1.36 ^{E-02}	3.06 ^{E-02}
GO:0033993	Response to lipid	5.35 ^{E-05}	1.92 ^{E-03}
GO:0009617	Response to bacterium	5.44 ^{E-05}	1.92 ^{E-07}
GO:1901701	Cellular response to oxygen-containing compound	6.659 ^{E-04}	4.05 ^{E-03}
GO:1902533	Positive regulation of intracellular signal transduction	5.44 ^{E-05}	6.42 ^{E-04}
GO:0010941	Regulation of cell death	9.92 ^{E-03}	4.20 ^{E-03}
GO:0071222	Cellular response to lipopolysaccharide	1.43 ^{E-05}	7.43 ^{E-03}
GO:0002521	Leukocyte differentiation	1.41 ^{E-04}	3.09 ^{E-02}
GO:0042531	Positive regulation of tyrosine phosphorylation of STAT protein	2.16 ^{E-05}	8.37 ^{E-03}
GO:0006959	Humoral immune response	7.46 ^{E-03}	2.53 ^{E-02}
GO:0050900	Leukocyte migration	3.14 ^{E-02}	1.00 ^{E-02}
GO:0098542	Defence response to other organism	5.78 ^{E-03}	1.16 ^{E-04}
GO:0033138	Positive regulation of peptidyl-serine phosphorylation	3.23 ^{E-03}	2.49 ^{E-02}
GO:0007259	JAK-STAT cascade	8.96 ^{E-04}	8.97 ^{E-03}

*No significant overlapping GO terms were found between the proteomic and transcriptomics pathways in the tocilizumab plus methotrexate arm. GO: gene ontology; FDR: false discovery rate.