

## Supplementary data:

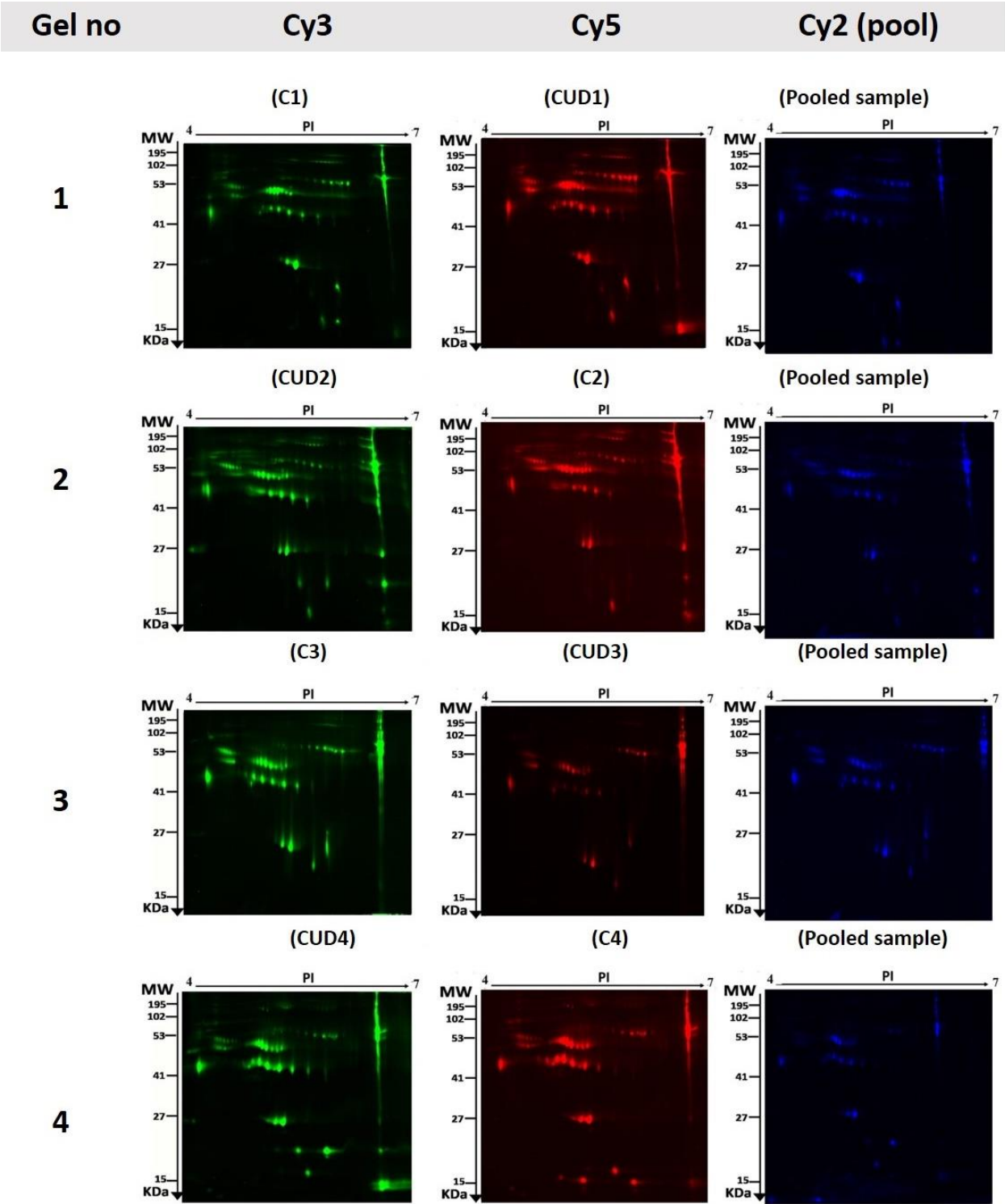
**Figure S1:** Pathways and canonical pathways identified in the IPA functional analysis.

Top Canonical Pathways		
Name	p-value	Overlap
LXR/RXR Activation	3.70E-16	11.0 % 13/118
FXR/RXR Activation	5.78E-16	10.7 % 13/122
Acute Phase Response Signaling	7.15E-14	7.4 % 13/176
Atherosclerosis Signaling	3.87E-07	5.6 % 7/126
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	4.24E-07	4.3 % 8/188

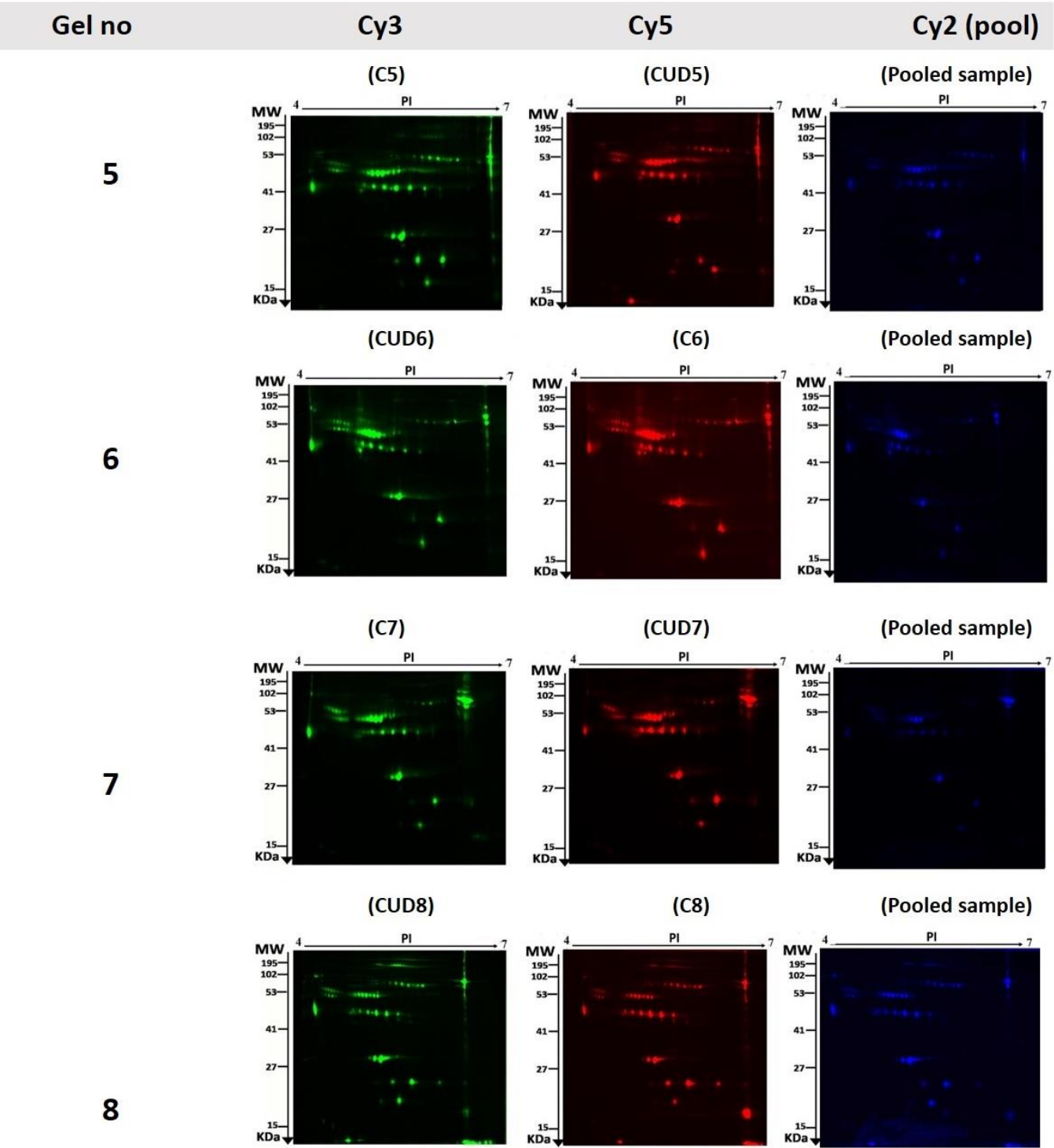
  

Top Networks		
ID	Associated Network Functions	Score
1	Free Radical Scavenging, Cellular Compromise, Inflammatory Response	52
2	Cell-To-Cell Signaling and Interaction, Hematological System Development and Function, Immune Cell Trafficking	26
3	Cancer, Hematological Disease, Immunological Disease	17
4	Cell Death and Survival, Skeletal and Muscular Disorders, Cancer	11

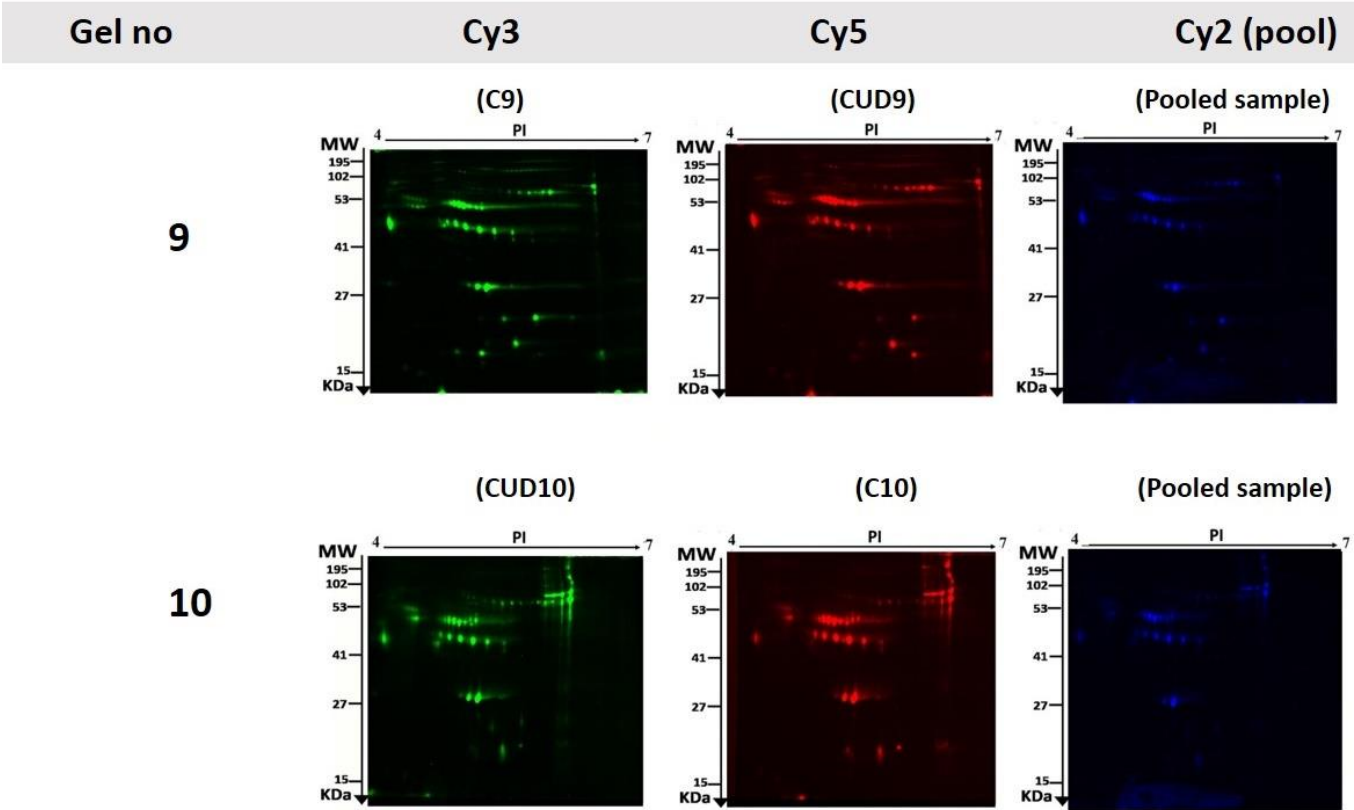
Figure S2: Gel images (n=10) of the study



CUD: Cannabis use disorder, C: Control samples

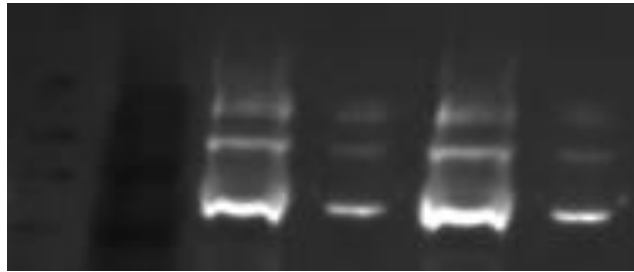


CUD: Cannabis use disorder, C: Control samples



CUD: Cannabis use disorder, C: Control samples

**Figure S3:** Example of the full western blots (not truncated)



**Table S1:** Dye-switching strategy applied during labeling to avoid dye-specific bias. A total of 20 patient samples were run on 10 2D-PAGE gels. Samples were labeled randomly with Cy3 and Cy5, and a pooled sample was used as an internal standard and was stained with Cy2 (CUD- Cannabis use disorder, C- Control).

Gel	Cy3	Cy5	Cy2
1	C1	CUD1	Pooled sample
2	CUD2	C2	Pooled sample
3	C3	CUD3	Pooled sample
4	CUD4	C4	Pooled sample
5	C5	CUD5	Pooled sample
6	CUD6	C6	Pooled sample
7	C7	CUD7	Pooled sample
8	CUD8	C8	Pooled sample
9	C9	CUD9	Pooled sample
10	CUD10	C10	Pooled sample

**Table S2:** List of significantly differentially abundant proteins between CUD patients and control samples identified in samples using 2D-DIGE coupled with MS. Protein name, accession number, Mascot score, MS coverage (64%), protein MW, and pI values according to Uniprot database are listed.

SI no:	Spot No <sup>a</sup>	Accession No <sup>b</sup>	Protein Name	MASCOT ID	Pi <sup>c</sup>	MW <sup>d</sup>	Cov%	Score <sup>e</sup>
1	253	Q9H792	Inactive tyrosine-protein kinase PEAK1	SG269_HUMAN	6.46	195039	15	56
2	1792	P02766	Transthyretin	TTHY_HUMAN	5.52	15991	69	92
3	202	P21580	Tumor necrosis factor alpha-induced protein 3	TNAP3_HUMAN	8.61	91837	17	60
4	860	P02787	Serotransferrin	TRFE_HUMAN	6.82	79280	21	143
5	1797	P13645	Keratin, type I cytoskeletal 10	K1C10_HUMAN	5.13	59020	22	96
6	1937	Q5T6V5	Queuosine salvage protein	CI064_HUMAN	5.61	39460	31	57
7	1082	O43300	Leucine-rich repeat transmembrane neuronal protein 2	LRRT2_HUMAN	8.27	59950	15	62
8	1226	Q9H254	Spectrin beta chain, non-erythrocytic 4	SPTN4_HUMAN	5.72	290005	15	63
9	1487	P01834	Immunoglobulin kappa constant	IGKC_HUMAN	5.58	11773	56	61
10	1470	P02647	Apolipoprotein A-I	APOA1_HUMAN	5.56	30759	72	160
11	382	P02787	Serotransferrin	TRFE_HUMAN	6.82	79280	27	97
12	1136	O75636	Ficolin-3	FCN3_HUMAN	6.20	33395	39	80
13	7	P02774	Vitamin D-binding protein	VTDB_HUMAN	5.40	54526	49	151
14	865	P00738	Haptoglobin	HPT_HUMAN	6.13	45861	27	91
15	864	P01024	Complement C3	CO3_HUMAN	6.02	188569	16	60
16	1322	P00739	Haptoglobin-related protein	HPTR_HUMAN	6.63	39518	25	63
17	857	Q07065	Cytoskeleton-associated protein 4	CKAP4_HUMAN	5.63	66097	18	57
18	385	P02787	Serotransferrin	TRFE_HUMAN	6.82	79280	62	234
19	820	Q14585	Zinc finger protein 345	ZN345_HUMAN	8.70	57229	26	56
20	1427	Q9BZ29	Dedicator of cytokinesis protein 9	DOCK9_HUMAN	7.25	238519	16	65
21	1120	O75648	Mitochondrial tRNA-specific 2-thiouridylase 1	MTU1_HUMAN	8.24	48284	21	57
22	1759	P02766	Transthyretin	TTHY_HUMAN	5.52	15991	69	135
23	1193	P04264	Keratin, type II cytoskeletal 1	K2C1_HUMAN	8.15	66170	34	85
24	108	O75121	Microfibrillar-associated protein 3-like	MFA3L_HUMAN	5.13	45750	19	58

25	185	P01011	Alpha-1-antichymotrypsin	AACT_HUMAN	5.33	47792	24	64
26	266	P02768	Albumin	ALBU_HUMAN	5.92	71371	53	133
27	235	P17039	Zinc finger protein 30	ZNF30_HUMAN	9.33	64035	34	62
28	357	P08631	Tyrosine-protein kinase HCK	HCK_HUMAN	6.27	60075	22	56
29	661	P01009	Alpha-1-antitrypsin	A1AT_HUMAN	5.37	46878	17	58
30	334	P02790	Hemopexin	HEMO_HUMAN	6.55	52385	36	131
31	450	P01009	Alpha-1-antitrypsin	A1AT_HUMAN	5.37	46878	49	133
32	1563	P18206	Vinculin	VINC_HUMAN	5.50	124292	11	666
33	853	P00738	Haptoglobin	HPT_HUMAN	6.13	45861	36	132
34	1448	Q6ZNG0	Zinc finger protein 620	ZN620_HUMAN	8.64	49612	22	61
35	1473	Q9HBT8	Zinc finger protein 286A	Z286A_HUMAN	8.64	61505	22	58
36	1231	P13645	Keratin, type I cytoskeletal 10	K1C10_HUMAN	5.13	59020	28	82
37	548	P02765	Alpha-2-HS-glycoprotein	FETUA_HUMAN	5.43	40098	33	60
38	497	P01009	Alpha-1-antitrypsin	A1AT_HUMAN	5.37	46878	40	88
39	1784	P02753	Retinol-binding protein 4	RET4_HUMAN	5.76	23337	76	74
40	1475	Q3L8U1	Chromodomain-helicase-DNA-binding protein 9	CHD9_HUMAN	6.56	327986	8	57
41	1295	Q969Q6	Serine/threonine-protein phosphatase 2A regulatory subunit B" subunit gamma	P2R3C_HUMAN	5.07	53567	26	60
42	1260	P02647	Apolipoprotein A-I	APOA1_HUMAN	5.56	30759	73	225
43	636	Q99661	Kinesin-like protein KIF2C	KIF2C_HUMAN	8.03	82174	18	57
44	1962	P13645	Keratin, type I cytoskeletal 10	K1C10_HUMAN	5.13	59020	17	63
45	456	Q9HAC8	Ubiquitin domain-containing protein 1	UBTD1_HUMAN	7.68	26150	16	57
46	1705	O15226	NF-kappa-B-repressing factor	NKRF_HUMAN	8.94	78308	16	60
47	1132	Q92896	Golgi apparatus protein 1	GSLG1_HUMAN	6.52	138341	31	61
48	1877	P20472	Parvalbumin alpha	PRVA_HUMAN	4.98	12051	58	68
49	504	Q08999	Retinoblastoma-like protein 2	RBL2_HUMAN	7.27	129711	26	73
50	1484	P02768	Albumin	ALBU_HUMAN	5.92	71371	80	230
51	1277	O75636	Ficolin-3	FCN3_HUMAN	6.20	33395	44	64
52	354	O60384	Putative zinc finger protein 861	YS022_HUMAN	8.91	12388	59	59
53	650	P01009	Alpha-1-antitrypsin	A1AT_HUMAN	5.37	46878	40	106
54	1037	Q14683	Structural maintenance of chromosomes protein 1A	SMC1A_HUMAN	7.51	143771	26	59
55	1138	Q6ZN19	Zinc finger protein 841	ZN841_HUMAN	9.48	95939	28	62
56	1669	P02753	Retinol-binding protein 4	RET4_HUMAN	5.76	23337	43	70
57	1446	Q9BV73	Centrosome-associated protein CEP250	CP250_HUMAN	5.00	281880	19	58
58	886	P00738	Haptoglobin	HPT_HUMAN	6.13	45861	19	58



59	457	Q96M63	Coiled-coil domain-containing protein 114	CC114_HUMAN	5.87	75172	24	67
60	522	Q9Y473	Zinc finger protein 175	ZN175_HUMAN	8.98	84009	41	82
61	1305	Q12852	Mitogen-activated protein kinase kinase kinase 12	M3K12_HUMAN	6.03	94130	11	56
62	1394	Q14204	Cytoplasmic dynein 1 heavy chain 1	DYHC1_HUMAN	6.01	534804	16	68
63	48	P49792	E3 SUMO-protein ligase RanBP2	RBP2_HUMAN	5.85	362365	14	65
64	903	O95389	Cellular communication network factor 6	WISP3_HUMAN	8.87	41319	28	66
65	28	Q14624	Inter-alpha-trypsin inhibitor heavy chain H4	ITI4_HUMAN	6.51	103521	26	81
66	1083	Q9UKX3	Myosin-13	MYH13_HUMAN	5.56	224681	19	65
67	1067	Q9NQW7	Xaa-Pro aminopeptidase 1	XPP1_HUMAN	5.42	70557	26	57
68	423	Q5R372	Rab GTPase-activating protein 1-like	RBG1L_HUMAN	5.18	70557	26	57
69	1213	Q14683	Structural maintenance of chromosomes protein 1A	SMC1A_HUMAN	7.51	143771	29	63
70	1180	Q8TED0	U3 small nucleolar RNA-associated protein 15 homolog	UTP15_HUMAN	9.18	58661	30	70
71	805	P04637	Cellular tumor antigen p53	P53_HUMAN	6.33	44196	22	56
72	388	P00751	Complement factor B	CFAB_HUMAN	6.67	86847	36	95
73	1106	Q8TD57	Dynein heavy chain 3, axonemal	DYH3_HUMAN	6.04	473776	14	64
74	579	P02768	Albumin	ALBU_HUMAN	5.92	71371	48	104
75	215	Q9Y4I1	Unconventional myosin-Va	MYO5A_HUMAN	8.70	216995	22	64
76	1865	P02766	Transthyretin	TTHY_HUMAN	5.52	15991	69	58
77	953	P00738	Haptoglobin	HPT_HUMAN	6.13	45861	39	92
78	528	P02768	Albumin	ALBU_HUMAN	5.92	71371	45	68
79	1627	P02647	Apolipoprotein A-I	APOA1_HUMAN	5.56	30759	33	76
80	1659	P02647	Apolipoprotein A-I	APOA1_HUMAN	5.56	30759	69	157
81	993	Q7Z398	Zinc finger protein 550	ZN550_HUMAN	8.95	49491	25	61
82	562	P19652	Alpha-1-acid glycoprotein 2	A1AG2_HUMAN	5.03	23873	42	85
83	974	P35558	Phosphoenolpyruvate carboxykinase, cytosolic [GTP]	PCKGC_HUMAN	5.80	69948	23	66
84	990	Q5BJF6	Outer dense fiber protein 2	ODFP2_HUMAN	7.53	96140	30	59
85	1211	P04264	Keratin, type II cytoskeletal 1	K2C1_HUMAN	8.15	66170	36	90
86	1054	Q9H792	Inactive tyrosine-protein kinase PEAK1	SG269_HUMAN	6.46	195039	18	71
87	955	Q5BJF6	Outer dense fiber protein 2	ODFP2_HUMAN	7.53	96140	36	93

88	2217	P68871	Hemoglobin subunit beta	HBB_HUMAN	6.76	16102	63	57
89	1039	P78332	RNA-binding protein 6	RBM6_HUMAN	5.93	129192	26	70
90	913	P02538	Keratin, type II cytoskeletal 6A	K2C6A_HUMAN	8.09	60239	35	80
91	604	Q6AW86	Zinc finger protein 324B	Z324B_HUMAN	9.78	61818	34	60
92	981	P06727	Apolipoprotein A-IV	APOA4_HUMAN	5.28	45371	41	128
93	1908	P02647	Apolipoprotein A-I	APOA1_HUMAN	5.56	30759	49	100
94	2323	P02042	Hemoglobin subunit delta	HBD_HUMAN	7.85	16159	63	61
95	481	Q5R372	Rab GTPase-activating protein 1-like	RBG1L_HUMAN	5.18	93366	16	59
96	623	Q92608	Dedicator of cytokinesis protein 2	DOCK2_HUMAN	6.43	213123	16	59
97	771	Q96EH8	E3 ubiquitin-protein ligase NEURL3	LINCR_HUMAN	8.36	29626	38	65
98	341	Q9P219	Protein Daple	DAPLE_HUMAN	5.87	229215	15	70
99	796	P00738	Haptoglobin	HPT_HUMAN	6.13	45861	33	95
100	987	Q709C8	Vacuolar protein sorting-associated protein 13C	VP13C_HUMAN	6.38	424462	12	68
101	732	P25311	Zinc-alpha-2-glycoprotein	ZA2G_HUMAN	5.57	34079	37	57
102	702	Q9UM13	Anaphase-promoting complex subunit 10	APC10_HUMAN	9.17	21410	22	63
103	533	P02774	Vitamin D-binding protein	VTDB_HUMAN	5.40	54526	26	69
104	1465	P17017	Zinc finger protein 14	ZNF14_HUMAN	9.36	77970	37	67
105	788	A8TX70	Collagen alpha-5(VI) chain	CO6A5_HUMAN	6.50	291796	15	58
106	584	Q8TD57	Dynein heavy chain 3, axonemal	DYH3_HUMAN	6.04	473776	13	60
107	1688	P20472	Parvalbumin alpha	PRVA_HUMAN	4.98	12051	57	56
108	633	P02768	Albumin	ALBU_HUMAN	5.92	71371	62	176
109	709	Q9NZM1	Myoferlin	MYOF_HUMAN	5.84	236100	18	70
110	198	P02768	Albumin	ALBU_HUMAN	5.92	71371	59	245
111	743	P01009	Alpha-1-antitrypsin	A1AT_HUMAN	5.37	46878	40	102
112	676	P02749	Beta-2-glycoprotein 1	APOH_HUMAN	8.34	39584	51	58
113	556	P20929	Nebulin	NEBU_HUMAN	9.11	775419	14	64
114	537	P02768	Albumin	ALBU_HUMAN	5.92	71371	53	114
115	714	Q02156	Protein kinase C epsilon type	KPCE_HUMAN	6.73	84989	24	71
116	588	Q96SZ6	Mitochondrial tRNA methyltransferase CDK5RAP1	CK5P1_HUMAN	8.52	68501	12	57
117	275	Q9Y473	Zinc finger protein 175	ZN175_HUMAN	8.98	84009	22	58
118	797	P00738	Haptoglobin	HPT_HUMAN	6.13	45861	35	94
119	768	O76041	Nebulette	NEBL_HUMAN	7.89	116609	21	62
120	550	Q8TE73	Dynein heavy chain 5, axonemal	DYH5_HUMAN	5.97	532504	17	60
121	549	P51508	Zinc finger protein 81	ZNF81_HUMAN	8.96	77679	29	67

<sup>a</sup> Spot number.

<sup>b</sup> Protein accession number for SWISSPROT Database.

<sup>c</sup> Theoretical isoelectric point.

<sup>d</sup> Theoretical relative mass.

<sup>e</sup> MASCOT score

**Table S3:** List of 25 proteins with accession numbers depicted in IPA network pathway

Sl no	Accession No	Protein Name	MASCOT ID
1	Q9Y4I1	Unconventional myosin-Va	MYO5A_HUMAN
2	P13645	Keratin, type I cytoskeletal 10 (KRT10*)	K1C10_HUMAN
3	Q08999	Retinoblastoma-like protein 2	RBL2_HUMAN
4	P04637	Cellular tumor antigen p53 (TP53)	P53_HUMAN
5	Q9Y473	Zinc finger protein 175	ZN175_HUMAN
6	P01011	Alpha-1-Antichymotrypsin (SERPINA3)	AACT_HUMAN
7	P18206	Vinculin (VCL)	VINC_HUMAN
8	P08631	Tyrosine-protein kinase (HCK)	HCK_HUMAN
9	Q02156	Protein kinase C epsilon Type (PRKCE)	KPCE_HUMAN
10	O15226	NF-kappa-B-repressing factor	NKRF_HUMAN
11	P21580	Tumor necrosis factor alpha-induced protein 3 (TNFAIP3)	TNAP3_HUMAN
12	P02753	Retinol-binding protein 4 (RBP4)	RET4_HUMAN
13	P25311	Zinc-alpha-2-Glycoprotein (AZGP1)	ZA2G_HUMAN
14	P02766	Transthyretin (TTR*)	TTHY_HUMAN
15	P01024	Complement C3 (C3)	CO3_HUMAN
16	P00751	Complement factor B (CFB)	CFAB_HUMAN
17	P02787	Serotransferrin (TF)	TRFE_HUMAN
18	P02768	Albumin (ALB)	ALBU_HUMAN
19	P68871	Hemoglobin subunit beta	HBB_HUMAN
20	P02647	Apolipoprotein A-I	APOA1_HUMAN
21	Q8TD57	Dynein heavy chain 3, Axonemal (DYNC1H1)	DYH3_HUMAN

22	P02790	Hemopexin (HPX)	HEMO_HUMAN
23	P06727	Apolipoprotein A-IV	APOA4_HUMAN
24	P00738	Haptoglobin (HP)	HPT_HUMAN
25	O95389	Cellular communication network factor 6 (CCN6)	WISP3_HUMAN

**Table S4:** List of proteins with accession numbers for the top 5 canonical pathways

	CANONICAL PATHWAYS	ACCESSION NUMBER	PROTEIN NAME
1	LXR/RXR Activation	P02765	Alpha-2-HS-glycoprotein
		P02768	Albumin
		P02647	Apolipoprotein A-I
		P06727	Apolipoprotein A-IV
		P02749	Beta-2-glycoprotein 1
		P01024	Complement C3
		P02774	Vitamin D-binding protein
		P00739	Haptoglobin-related protein
		P02790	Hemopexin
		Q14624	Inter-alpha-trypsin inhibitor heavy chain H4
		P19652	Alpha-1-acid glycoprotein 2
		P02753	Retinol-binding protein 4
		P01009	Alpha-1-antitrypsin
		P02787	Serotransferrin
		P02766	Transthyretin
2	FXR/RXR Activation	P02765	Alpha-2-HS-glycoprotein
		P02768	Albumin
		P02647	Apolipoprotein A-I
		P06727	Apolipoprotein A-IV
		P02749	Beta-2-glycoprotein 1
		P01024	Complement C3
		P02774	Vitamin D-binding protein
		P00739	Haptoglobin-related protein
		P02790	Hemopexin
		Q14624	Inter-alpha-trypsin inhibitor heavy chain H4
		P19652	Alpha-1-acid glycoprotein 2
		P02753	Retinol-binding protein 4
		P01009	Alpha-1-antitrypsin
		P02787	Serotransferrin
		P02766	Transthyretin
3	Acute Phase Response Signaling	P02765	Alpha-2-HS-glycoprotein
		P02768	Albumin
		P02647	Apolipoprotein A-I

		P02749	Beta-2-glycoprotein 1
		P01024	Complement C3
		P00751	Complement factor B
		P00738	Haptoglobin
		P02790	Hemopexin
		Q14624	Inter-alpha-trypsin inhibitor heavy chain H4
		P19652	Alpha-1-acid glycoprotein 2
		P02753	Retinol-binding protein 4
		P01009	Alpha-1-antitrypsin
		P01011	Alpha-1- antichymotrypsin
		P02787	Serotransferrin
		P02766	Transthyretin
4	<b>Production of Nitric oxide and Reactive Oxygen Species</b>	P02768	Albumin
		P02647	Apolipoprotein A-I
		P06727	Apolipoprotein A-IV
		Q12852	Mitogen-activated protein kinase kinase 12
		P19652	Alpha-1-acid glycoprotein 2
		Q02156	Protein kinase C epsilon type
		P02753	Retinol-binding protein 4
		P01009	Alpha-1-antitrypsin
5	<b>Atherosclerosis Signaling</b>	P02768	Albumin
		P02647	Apolipoprotein A-I
		P06727	Apolipoprotein A-IV
		Q92896	Golgi apparatus protein 1
		P19652	Alpha-1-acid glycoprotein 2
		P02753	Retinol-binding protein 4
		P01009	Alpha-1-antitrypsin