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Computational Discovery of an AI-Driven Dexamethasone Derivative for Parkinson’s disease: Network Pharmacology, Docking, and MD Simulations

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Parkinson's disease (PD) is a complex neurodegenerative disorder with few treatment options that are responsible for only slowing the disease progression. Several studies observed that dexamethasone exhibits neuroprotective effects; however, its systemic side effects restrict its use for prolonged periods. Our study employed Webserver-Aided Drug Design by Artificial Intelligence and Classical Algorithm (WDDAICA) to generate novel dexamethasone analogues with improved pharmacological properties suitable for PD therapy. Differentially expressed genes (DEGs) from the transcriptome data of PD patients (GSE160299) have been compared with dexamethasone-responsive genes, resulting in the identification of 92 shared targets. Enrichment analysis identified essential molecular functions, including metal ion binding and enzyme regulation, highlighting APOE, ICAM1, GAPDH, and EGF as critical targets. The AI-generated derivatives were evaluated using molecular docking against these targets, with molecule C displaying the best binding affinity to APOE (−7.6 kcal/mol), passing dexamethasone (−7.2 kcal/mol). ADMET profiling shows improved oral bioavailability and blood-brain barrier (BBB) permeability for molecule C; however, it also indicates elevated risk for hepatic damage. Molecular dynamics (MD) simulations validated enhanced structural stability and compactness of the molecule C–APOE complex. Additionally, MM-PBSA free energy assessments indicated a superior binding energy for molecule C (−13.8 kcal/mol) in contrast to dexamethasone (−1.8 kcal/mol), accompanied by more comprehensive per-residue interactions. The data indicates that molecule C may be an acceptable candidate for subsequent in vivo study as a neuroprotective drug in PD.

Keyworks: Parkinson's disease; APOE; Dexamethasone; AI Drug Design; Molecular Dynamics Simulations

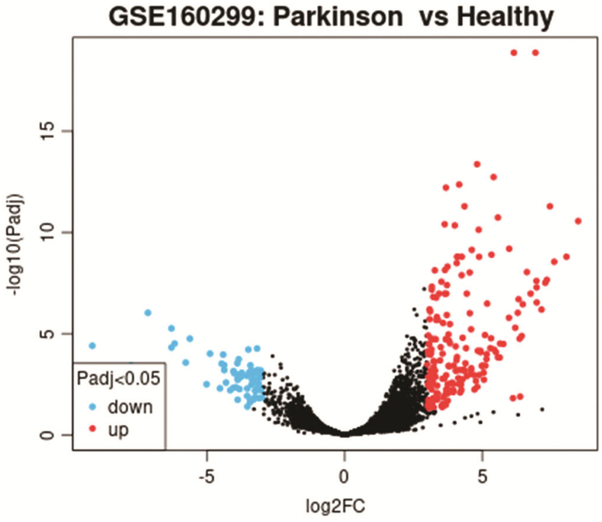

Figure S1 — Differentially expressed genes in Parkinson’s disease vs Healthy: Volcano plot analysis.

Table S1 —DEGs from GSE160299 ($log_2FC \geq 3$; adj. $p < 0.05$) in PD vs. healthy plasma samples.

Symbol	Description	log2 (fold change) (Parkinson vs Healthy)	log10 (P-value) (Parkinson vs Healthy)
UMOD	uromodulin	-9.181	4.401
SLC12A1	solute carrier family 12 member 1	-7.772	3.426
AQP2	aquaporin 2	-7.157	6.029
LOC112267905	replaced by ID 105370807	-6.302	5.26
KNG1	kininogen 1	-6.301	4.314
LOC107984758	Predicted gene (uncharacterized)	-6.187	4.51
LOC107984756	Predicted gene (uncharacterized)	-5.783	3.57
AQP5-AS1	AQP5 and AQP2 antisense RNA 2	-5.631	4.752
CLDN8	claudin 8	-5.025	2.5
LOC107984755	uncharacterized LOC107984755	-4.899	4.011
RANBP3L	RAN binding protein 3 like	-4.538	2.299
DUSP9	dual specificity phosphatase 9	-4.476	3.515
CLCNKB	Chloride voltage-gated channel Kb	-4.42	3.964
CLCNKA	chloride voltage-gated channel Ka	-4.386	3.447
PRDM16-DT	PRDM16 divergent transcript	-4.381	3.2
FXYD4	FXYD domain containing ion transport regulator 4	-4.318	2.581
AIF1L	allograft inflammatory factor 1 like	-4.166	2.208
EGF	epidermal growth factor	-4.047	2.329
TRNQ	tRNA-Gln	-4.042	3.149
TRNI	tRNA-Ile	-4.017	3.043
ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide	-3.957	2.353
PTGER1	prostaglandin E receptor 1	-3.904	3.536
SCNN1A	sodium channel epithelial 1 subunit alpha	-3.895	2.785
MAL	mal, T cell differentiation protein	-3.894	1.735
TRNM	tRNA-Met	-3.892	2.721
TRNL2	tRNA-Leu	-3.89	2.975
TMEM72	transmembrane protein 72	-3.856	3.737
MFSD4A	major facilitator superfamily domain containing 4A	-3.827	2.262
KCNJ1	potassium inwardly rectifying channel subfamily J member 1	-3.801	2.842
TRNR	tRNA-Arg	-3.788	2.945
TRNS2	tRNA-Ser	-3.772	2.898
TRND	tRNA-Asp	-3.744	3.068
TRNH	tRNA-His	-3.562	2.915
TMEM213	transmembrane protein 213	-3.547	1.923
SFRP1	secreted frizzled related protein 1	-3.544	2.291
HSD11B2	hydroxysteroid 11-beta dehydrogenase	-3.54	1.4
RNR2	l-rRNA	-3.505	4.217
ND1	NADH dehydrogenase subunit 1	-3.472	3.091
DEFB1	defensin beta 1	-3.447	1.611
MFSD4A-AS1	MFSD4A antisense RNA 1	-3.44	1.751
RNR1	s-rRNA	-3.43	3.436
SIM2	SIM bHLH transcription factor 2	-3.39	3.2
TRNT	tRNA-Thr	-3.39	2.483
TRNW	tRNA-Trp	-3.375	2.748
TRNL1	tRNA-Leu	-3.344	2.788
GP2	glycoprotein 2	-3.333	3.013
GPC3	glypican 3	-3.323	1.737
TRNK	tRNA-Lys	-3.28	2.614
TRNF	tRNA-Phe	-3.266	1.864
SPTBN2	spectrin beta, non-erythrocytic 2	-3.255	2.19
TRNV	tRNA-Val	-3.248	2.177
TRNG	tRNA-Gly	-3.23	2.704

(*Contd.*)

Table S1 —DEGs from GSE160299 ($\log_2FC \geq 3$; adj. $p < 0.05$) in PD vs. healthy plasma samples — (*Contd.*)

Symbol	Description	log2 (fold change) (Parkinson vs Healthy)	log10 (P-value) (Parkinson vs Healthy)
ND3	NADH dehydrogenase subunit 3	-3.189	4.265
TFCP2L1	transcription factor CP2 like 1	-3.182	2.312
LOC107985492	uncharacterized LOC107985492	-3.181	3.052
ATP8	ATP synthase F0 subunit 8	-3.172	3.2
LINC01762	long intergenic non-protein coding RNA 1762	-3.157	2.253
ADGRF1	adhesion G protein-coupled receptor F1	-3.136	2.451
PWRN1	Prader-Willi region non-protein coding RNA 1	-3.134	1.816
PROM2	prominin 2	-3.133	2.563
ND4L	NADH dehydrogenase subunit 4L	-3.121	3.013
ND5	NADH dehydrogenase subunit 5	-3.081	2.854
ATP6	ATP synthase F0 subunit 6	-3.055	3.179
CLDN19	claudin 19	-3.053	2.204
KLRG2	killer cell lectin like receptor G2	-3.013	1.84
TYMP	thymidine phosphorylase	3.001	3.474
IGLC5	immunoglobulin lambda constant 5 (pseudogene)	3.004	1.473
SPAG4	sperm associated antigen 4	3.018	4.125
CD14	CD14 molecule	3.025	2.5
KDR	kinase insert domain receptor	3.03	2.864
CFI	complement factor I	3.036	1.727
HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	3.036	2.477
ZNF395	zinc finger protein 395	3.04	4.908
TYROBP	transmembrane immune signaling adaptor TYROBP	3.054	4.481
CLDN1	claudin 1	3.058	1.407
PLOD1	procollagen-lysine,2-oxoglutarate 5-dioxygenase 1	3.059	3.975
RPS19	ribosomal protein S19	3.06	1.317
ELK2AP	ETS transcription factor ELK2A, pseudogene	3.071	1.382
LOC112267910	NACHT, LRR and PYD domains-containing protein 10-like	3.074	4.492
CCND1	cyclin D1	3.077	2.377
TRIB3	tribbles pseudokinase 3	3.085	6.2
SCARB1	scavenger receptor class B member 1	3.087	5.713
ENO2	enolase 2	3.106	6.094
UGT1A8	UDP glucuronosyltransferase family 1 member A8	3.112	3.172
CD36	CD36 molecule	3.116	2.968
SLC2A1	solute carrier family 2 member 1	3.118	3.964
ICAM1	intercellular adhesion molecule 1	3.125	2.556
UGT1A7	UDP glucuronosyltransferase family 1 member A7	3.141	4.049
MT1F	metallothionein 1F	3.143	1.62
HSPB8	heat shock protein family B (small) member 8	3.144	4.755
CLDN2	claudin 2	3.144	1.714
IKBIP	IKBKB interacting protein	3.154	4.226
LINC00887	long intergenic non-protein coding RNA 887	3.16	7.172
KISS1R	KISS1 receptor	3.16	2.746
TP53INP1	tumor protein p53 inducible nuclear protein 1	3.162	2.236

(*Contd.*)

Table S1 —DEGs from GSE160299 ($log_2FC \geq 3$; adj. $p < 0.05$) in PD vs. healthy plasma samples — (*Contd.*)

Symbol	Description	log2 (fold change) (Parkinson vs Healthy)	log10 (P-value) (Parkinson vs Healthy)
STC2	stanniocalcin 2	3.165	7.32
CD79A	CD79a molecule	3.166	1.687
MAP7D2	MAP7 domain containing 2	3.17	2.597
IGHV1-18	immunoglobulin heavy variable 1-18	3.186	1.61
LRP2	LDL receptor related protein 2	3.195	3.204
RAB42	RAB42, member RAS oncogene family	3.202	2.657
LOC105374709	uncharacterized LOC105374709	3.204	2.512
IGLV1-36	immunoglobulin lambda variable 1-36	3.205	1.783
FOLH1	folate hydrolase 1	3.216	6.819
IGKV1-27	immunoglobulin kappa variable 1-27	3.225	1.815
CES4A	carboxylesterase 4A	3.226	3.648
CLRN3	clarin 3	3.233	3.349
GAPDH	glyceraldehyde-3-phosphate dehydrogenase	3.233	1.363
SERPINE2	serpin family E member 2	3.239	3.071
KMO	kynurenine 3-monooxygenase	3.247	4.722
GSTA1	glutathione S-transferase alpha 1	3.271	3.602
ANPEP	alanyl aminopeptidase, membrane	3.276	8.126
HILPDA-AS1	HILPDA antisense RNA 1	3.282	4.721
NMB	neuromedin B	3.282	3.164
CYBA	cytochrome b-245 alpha chain	3.298	2.872
C1QB	complement C1q B chain	3.308	4.721
BHLHE41	basic helix-loop-helix family member e41	3.323	5.676
C1QC	complement C1q C chain	3.324	6.777
IGHV4-4	immunoglobulin heavy variable 4-4	3.341	2.054
UGT1A9	UDP glucuronosyltransferase family 1 member A9	3.348	5.823
SLC2A3	solute carrier family 2 member 3	3.349	1.746
HPS3	HPS3 biogenesis of lysosomal organelles complex 2 subunit 1	3.362	2.433
DEGS1	delta 4-desaturase, sphingolipid 1	3.369	2.048
MT1E	metallothionein 1E	3.378	2.014
PRDX4	peroxiredoxin 4	3.386	1.785
CD68	CD68 molecule	3.391	5.676
ACKR3	atypical chemokine receptor 3	3.423	6.975
SOCS3	suppressor of cytokine signaling 3	3.469	3.68
UGT1A6	UDP glucuronosyltransferase family 1 member A6	3.489	4.336
IGHV3-73	immunoglobulin heavy variable 3-73	3.514	1.434
HAVCR2	hepatitis A virus cellular receptor 2	3.515	7.566
MT2A	metallothionein 2A	3.552	2.773
RGS5	regulator of G protein signaling 5	3.553	1.37
MS4A7	membrane spanning 4-domains A7	3.554	4.011
IGHV1-24	immunoglobulin heavy variable 1-24	3.574	1.546
KCNE3	potassium voltage-gated channel subfamily E regulatory subunit 3	3.577	5.522
IGKV2-30	immunoglobulin kappa variable 2-30	3.588	1.87
DDIT4	DNA damage inducible transcript 4	3.615	2.785
C4A	complement C4A (Rodgers blood group)	3.631	6.975
SLC16A1	solute carrier family 16 member 1	3.632	10.402
ST8SIA4	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4	3.646	8.14
VMP1	vacuole membrane protein 1	3.666	2.019
IGKV1-33	immunoglobulin kappa variable 1-33	3.674	1.477
BHMT	betaine--homocysteine S-methyltransferase	3.677	4.721

(*Contd.*)

Table S1 —DEGs from GSE160299 ($\log_2FC \geq 3$; adj. $p < 0.05$) in PD vs. healthy plasma samples — (*Contd.*)

Symbol	Description	log2 (fold change) (Parkinson vs Healthy)	log10 (P-value) (Parkinson vs Healthy)
ARL4C	ADP ribosylation factor like GTPase 4C	3.68	12.21
GJA1	gap junction protein alpha 1	3.682	4.722
PROS1	protein S	3.689	2.946
SERPINF2	serpinfamily F member 2	3.692	6.975
ANKRD36BP2	ankyrin repeat domain 36B pseudogene 2	3.697	2.205
MIR650	microRNA 650	3.704	2.264
C1QA	complement C1q A chain	3.71	5.92
C4B	complement C4B (Chido blood group)	3.715	7.399
CXCR4	C-X-C motif chemokine receptor 4	3.736	8.312
SPARC	secreted protein acidic and cysteine rich	3.741	2.512
TMSB10	thymosin beta 10	3.746	1.687
IGKV2-28	immunoglobulin kappa variable 2-28	3.761	2.064
IGFBP1	insulin like growth factor binding protein 1	3.766	2.203
TGFA	transforming growth factor alpha	3.77	3.404
SLC2A5	solute carrier family 2 member 5	3.772	4.96
SERPINE1	serpin family E member 1	3.79	4.658
PREX2	phosphatidylinositol-3,4,5-trisphosphate dependent Rac exchange factor 2	3.808	3.392
PCSK6	proprotein convertase subtilisin/kexin type 6	3.825	5.471
FLT1	fms related receptor tyrosine kinase 1	3.826	4.524
IGLV2-8	immunoglobulin lambda variable 2-8	3.854	2.524
IGHV3-15	immunoglobulin heavy variable 3-15	3.907	2.579
SPP1	secreted phosphoprotein 1	3.908	2.185
IGHV3-30	immunoglobulin heavy variable 3-30	3.942	2.114
MZB1	marginal zone B and B1 cell specific protein	3.953	2.506
IGHV7-4-1	immunoglobulin heavy variable 7-4-1	3.955	2.205
POSTN	periostin	4.004	10.347
PIM2	Pim-2 proto-oncogene, serine/threonine kinase	4.032	4.371
AQP9	aquaporin 9	4.034	3.168
PLOD2	procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	4.063	3.689
VWF	von Willebrand factor	4.07	8.489
TGFBI	transforming growth factor beta induced	4.083	3.846
ENPEP	glutamyl aminopeptidase	4.088	8.796
LUCAT1	lung cancer associated transcript 1	4.106	8.796
ALB	albumin	4.13	2.802
LYZ	lysozyme	4.132	3.2
HMOX1	heme oxygenase 1	4.16	12.367
IGHV3-23	immunoglobulin heavy variable 3-23	4.165	2.5
IGLV2-28	immunoglobulin lambda variable 2-28 (pseudogene)	4.193	2.672
IGLV1-40	immunoglobulin lambda variable 1-40	4.194	2.096
IGLC6	immunoglobulin lambda constant 6	4.23	2.482
IGKV1-12	immunoglobulin kappa variable 1-12	4.243	2.22
IGLJ3	immunoglobulin lambda joining 3	4.244	3.2
IGHV4-59	immunoglobulin heavy variable 4-59	4.246	2.704
APOC1	apolipoprotein C1	4.251	7.886
CA9	carbonic anhydrase 9	4.258	8.796
IGHV4-39	immunoglobulin heavy variable 4-39	4.277	2.746
RGS1	regulator of G protein signaling 1	4.288	4.797
VCAM1	vascular cell adhesion molecule 1	4.331	3.213
NPTX2	neuronal pentraxin 2	4.353	11.29
IGKV3D-15	immunoglobulin kappa variable 3D-15	4.364	3.157

(*Contd.*)

Table S1 —DEGs from GSE160299 ($\log_2 FC \geq 3$; adj. $p < 0.05$) in PD vs. healthy plasma samples — (*Contd.*)

Symbol	Description	log2 (fold change) (Parkinson vs Healthy)	log10 (P-value) (Parkinson vs Healthy)
IGKV2D-28	immunoglobulin kappa variable 2D-28	4.385	3.536
HHLA2	HERV-H LTR-associating 2	4.409	4.282
ADM	adrenomedullin	4.436	6.975
PLIN2	perilipin 2	4.44	2.899
CDH6	cadherin 6	4.542	8.02
VEGFA	vascular endothelial growth factor A	4.55	6.008
IGHV3-7	immunoglobulin heavy variable 3-7	4.576	3.008
IGLV1-51	immunoglobulin lambda variable 1-51	4.586	3.213
SLC39A14	solute carrier family 39 member 14	4.593	5.214
IGFBP3	insulin like growth factor binding protein 3	4.6	3.287
EGLN3	egl-9 family hypoxia inducible factor 3	4.618	9.138
MT1G	metallothionein 1G	4.701	2.957
IGLV2-33	immunoglobulin lambda variable 2-33 (non-functional)	4.714	2.238
IGHV1-3	immunoglobulin heavy variable 1-3	4.771	2.667
NDUFA4L2	NDUFA4 mitochondrial complex associated like 2	4.814	13.368
IGLC7	immunoglobulin lambda constant 7	4.82	2.377
IGLV3-1	immunoglobulin lambda variable 3-1	4.838	4.152
SCD	stearoyl-CoA desaturase	4.87	10.132
IGKV3-15	immunoglobulin kappa variable 3-15	4.883	2.957
ESM1	endothelial cell specific molecule 1	4.886	8.796
IGKV1D-39	immunoglobulin kappa variable 1D-39	4.935	4.152
IGKV1-39	immunoglobulin kappa variable 1-39	4.942	4.082
COL8A1	collagen type VIII alpha 1 chain	4.965	3.421
IGLV3-21	immunoglobulin lambda variable 3-21	4.981	3.408
IGLV2-11	immunoglobulin lambda variable 2-11	5.02	3.404
IGKV1-17	immunoglobulin kappa variable 1-17	5.051	3.073
IGLC3	immunoglobulin lambda constant 3 (Kern-Oz+ marker)	5.06	2.724
SERPINA1	serpin family A member 1	5.098	4.928
IGHV3-33	immunoglobulin heavy variable 3-33	5.116	3.421
IGLJ1	immunoglobulin lambda joining 1	5.15	3.742
IGKV3-11	immunoglobulin kappa variable 3-11	5.165	3.994
IGHA2	immunoglobulin heavy constant alpha 2 (A2m marker)	5.176	6.484
IGKV1-9	immunoglobulin kappa variable 1-9	5.293	4.282
FGA	fibrinogen alpha chain	5.317	4.771
LOX	lysyl oxidase	5.336	8.899
NNMT	nicotinamide N-methyltransferase	5.412	12.734
IGLV2-14	immunoglobulin lambda variable 2-14	5.431	4.215
IGKV1-5	immunoglobulin kappa variable 1-5	5.498	4.082
ENPP3	ectonucleotide pyrophosphatase/phosphodiesterase 3	5.57	10.736
IGLV3-19	immunoglobulin lambda variable 3-19	5.57	3.827
IGLJ2	immunoglobulin lambda joining 2	5.635	3.82
IGLL5	immunoglobulin lambda like polypeptide 5	5.643	4.51
IGHJ5	immunoglobulin heavy joining 5	5.768	4.492
IGLV2-23	immunoglobulin lambda variable 2-23	5.971	5.781
APOE	apolipoprotein E	5.978	9.196
IGKV3-20	immunoglobulin kappa variable 3-20	6.117	1.811
C3	complement C3	6.151	18.878
IGHGP	immunoglobulin heavy constant gamma P (non-functional)	6.198	5.29
IGHJ3	immunoglobulin heavy joining 3	6.291	6.029

(*Contd.*)

Table S1 —DEGs from GSE160299 ($log_2FC \geq 3$; adj. $p < 0.05$) in PD vs. healthy plasma samples — (*Contd.*)

Symbol	Description	log2 (fold change) (Parkinson vs Healthy)	log10 (P-value) (Parkinson vs Healthy)
IGHG3	immunoglobulin heavy constant gamma 3 (G3m marker)	6.32	6.7
IGHV3-11	immunoglobulin heavy variable 3-11	6.359	4.752
IGKJ4	immunoglobulin kappa joining 4	6.379	1.892
IGHV1-46	immunoglobulin heavy variable 1-46	6.435	4.883
IGHJ6	immunoglobulin heavy joining 6	6.472	6.453
IGKV4-1	immunoglobulin kappa variable 4-1	6.623	8.041
FGB	fibrinogen beta chain	6.758	6.975
ANGPTL4	angiopoietin like 4	6.936	18.878
FGG	fibrinogen gamma chain	6.971	7.604
IGLC1	immunoglobulin lambda constant 1	6.975	7.286
IGKC	immunoglobulin kappa constant	6.981	6.539
IGHG1	immunoglobulin heavy constant gamma 1 (G1m marker)	7.154	6.19
IGHG4	immunoglobulin heavy constant gamma 4 (G4m marker)	7.292	7.513
IGLC2	immunoglobulin lambda constant 2	7.35	7.656
IGHA1	immunoglobulin heavy constant alpha	7.461	11.29
CCL20	C-C motif chemokine ligand 20	7.616	8.551
IGKJ2	immunoglobulin kappa joining 2	8.061	8.796
IGHG2	immunoglobulin heavy constant gamma 2 (G2m marker)	8.488	10.561

Table S2 — Total gene ontology and pathway enrichment analysis.

Term	Count	P-Value	Fold Enrichment	Enrichment Log 2
extracellular space	14	3.83E-10	7.80	2.96
platelet alpha granule lumen	5	3.91E-07	76.45	6.26
extracellular exosome	12	7.40E-07	5.57	2.48
Glycoprotein	18	7.78E-07	2.66	1.41
Secreted	12	2.75E-06	4.88	2.29
Protein N-linked glycosylation	14	1.40E-05	3.27	1.71
positive regulation of angiogenesis	5	1.58E-05	30.25	4.92
integrin binding	5	1.62E-05	30.08	4.91
Immunoglobulin-like domain binding	4	1.87E-05	72.54	6.18
cell surface	7	1.94E-05	10.99	3.46
collagen-containing extracellular matrix	6	2.04E-05	16.12	4.01
hsa04510:Focal adhesion	6	3.55E-05	14.01	3.81
positive regulation of endothelial cell migration	4	3.62E-05	58.14	5.86
HIF-1 signaling pathway	5	5.47E-05	21.55	4.43
Ig-like C2-type 4	4	5.77E-05	49.82	5.64
low-density lipoprotein particle clearance	3	8.15E-05	208.69	7.71
extracellular region	10	8.35E-05	4.50	2.17
KW-0732~Signal	14	1.10E-04	2.58	1.37
angiogenesis	5	1.14E-04	18.24	4.19
plasma membrane	14	1.88E-04	2.60	1.38
Ig-like C2-type 7	3	2.00E-04	134.84	7.08
Ig-like C2-type 3	4	2.34E-04	31.09	4.96
KW-1015~Disulfide bond	14	2.51E-04	2.53	1.34
negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	3	3.86E-04	97.39	6.61
small molecule binding	3	4.50E-04	90.25	6.50
cellular response to vascular endothelial growth factor stimulus	3	4.67E-04	88.54	6.47
external side of plasma membrane	5	4.69E-04	12.59	3.65
PI3K-Akt signaling pathway	6	5.42E-04	7.86	2.97
Ig-like C2-type 6	3	5.81E-04	79.52	6.31
negative regulation of endothelial cell apoptotic process	3	5.88E-04	78.96	6.30
KW-0945~Host-virus interaction	6	6.74E-04	7.11	2.83
cellular response to amyloid-beta	3	9.49E-04	62.16	5.96
AGE-RAGE signaling pathway in diabetic complications	4	9.70E-04	18.78	4.23
Ig-like C2-type 1	4	0.0010	18.88	4.24
Ig-like C2-type 2	4	0.0010	18.88	4.24
positive regulation of ERK1 and ERK2 cascade	4	0.0010	18.82	4.23
lipid binding	4	0.0012	17.99	4.17
platelet-derived growth factor receptor-beta signaling pathway	3	0.0013	54.11	5.76
Cell adhesion	5	0.0018	8.33	3.06
CD36/SCARB1/SNMP1	2	0.0018	1040.40	10.02
cell adhesion	5	0.0018	8.71	3.12
collagen binding	3	0.0021	41.26	5.37
Fluid shear stress and atherosclerosis	4	0.0025	13.45	3.75
positive regulation of cell migration	4	0.0026	13.53	3.76
VEGFR1-3_5th	2	0.0027	693.60	9.44
CD36_fam	2	0.0027	693.60	9.44
VEGFR1-3_N_Ig-like	2	0.0027	693.60	9.44
VEGFR-2_TMD	2	0.0027	693.60	9.44
KW-0186~Copper	3	0.0027	32.80	5.04
early endosome	4	0.0028	13.20	3.72
Golgi apparatus	6	0.0028	5.56	2.48
Host cell receptor for virus entry	3	0.0028	34.61	5.11
Ig-like_fold	6	0.0028	5.54	2.47
endoplasmic reticulum lumen	4	0.0029	13.08	3.71

(*Contd.*)

Table S2 — Total gene ontology and pathway enrichment analysis.

Term	Count	P-Value	Fold Enrichment	Enrichment Log 2
virus receptor activity	3	0.0029	35.22	5.14
adhesion of symbiont to host	2	0.0029	649.27	9.34
amyloid-beta binding	3	0.0031	33.98	5.09
cell chemotaxis	3	0.0032	33.58	5.07
Extracellular	9	0.0034	3.09	1.63
plasma lipoprotein particle clearance	2	0.0039	486.95	8.93
endoplasmic reticulum	6	0.0039	5.14	2.36
Malaria	3	0.0043	28.45	4.83
epidermal growth factor receptor signaling pathway	3	0.0045	28.37	4.83
Cholesterol metabolism	3	0.0045	27.89	4.80
Cytoplasmic	10	0.0046	2.64	1.40
Immunoglobulin_dom	3	0.0047	27.62	4.79
symbiont entry into host cell	3	0.0048	27.31	4.77
regulation of bone development	2	0.0049	389.56	8.61
lipid transport	3	0.0050	26.80	4.74
receptor ligand activity	3	0.0054	25.79	4.69
ICAM_VCAM	2	0.0055	346.80	8.44
ICAM_VCAM_N	2	0.0055	346.80	8.44
Endosome	5	0.0055	6.43	2.68
membrane to membrane docking	2	0.0058	324.63	8.34
Cells and Molecules involved in local acute inflammatory response	3	0.0064	22.02	4.46
positive regulation of protein phosphorylation	3	0.0066	23.19	4.54
cholesterol import	2	0.0068	278.26	8.12
high-density lipoprotein particle clearance	2	0.0068	278.26	8.12
Malaria, cerebral, susceptibility to	2	0.0069	271.24	8.08
CARBOHYD:O-linked (GalNAc...) threonine	3	0.0070	22.47	4.49
Ig_I-set	3	0.0074	21.83	4.45
positive regulation of cholesterol storage	2	0.0078	243.48	7.93
lipoprotein particle binding	2	0.0079	240.66	7.91
blood microparticle	3	0.0079	21.08	4.40
Tyr_kinase_rcpt_3_CS	2	0.0082	231.20	7.85
18.Cytokine_astocytes	3	0.0091	14.55	3.86
CARBOHYD:N-linked (Glc) (glycation) lysine	2	0.0092	206.75	7.69
nitric oxide-cGMP-mediated signaling	2	0.0097	194.78	7.61
cholesterol catabolic process	2	0.0097	194.78	7.61
Ig_sub	4	0.0118	7.84	2.97
positive regulation of phagocytosis, engulfment	2	0.0126	149.83	7.23
high-density lipoprotein particle binding	2	0.0128	148.10	7.21
Complement and coagulation cascades	3	0.0129	16.16	4.01
Calcium signaling pathway	4	0.0130	7.47	2.90
ECM-receptor interaction	3	0.0132	15.98	4.00
protein binding	19	0.0134	1.34	0.42
cellular response to oxidised low-density lipoprotein particle stimulus	2	0.0136	139.13	7.12
negative regulation of blood coagulation	2	0.0136	139.13	7.12
cellular response to lipopolysaccharide	3	0.0148	15.22	3.93
platelet alpha granule	2	0.0154	122.32	6.93
platelet alpha granule membrane	2	0.0154	122.32	6.93
endothelial cell differentiation	2	0.0155	121.74	6.93
positive regulation of blood coagulation	2	0.0155	121.74	6.93
long-chain fatty acid transport	2	0.0155	121.74	6.93
membrane raft	3	0.0156	14.78	3.89
reverse cholesterol transport	2	0.0165	114.58	6.84
receptor complex	3	0.0165	14.37	3.85
positive regulation of phosphatidylinositol 3-kinase/protein kinase B signal transduction	3	0.0166	14.32	3.84
positive regulation of MAPK cascade	3	0.0166	14.32	3.84

(*Contd*.)

Table S2 — Total gene ontology and pathway enrichment analysis.

Term	Count	P-Value	Fold Enrichment	Enrichment Log 2
low-density lipoprotein particle binding	2	0.0167	113.25	6.82
Glycation	2	0.0171	110.12	6.78
extracellular matrix	3	0.0174	13.99	3.81
mammary gland alveolus development	2	0.0174	108.21	6.76
negative regulation of endopeptidase activity	2	0.0174	108.21	6.76
endocytic vesicle lumen	2	0.0181	103.98	6.70
blood vessel morphogenesis	2	0.0184	102.52	6.68
SM00409:IG	4	0.0191	6.20	2.63
high-density lipoprotein particle remodeling	2	0.0203	92.75	6.54
response to steroid hormone	2	0.0203	92.75	6.54
antioxidant activity	2	0.0205	91.68	6.52
positive regulation of canonical NF-kappaB signal transduction	3	0.0211	12.59	3.65
regulation of protein-containing complex assembly	2	0.0213	88.54	6.47
Leukocyte transendothelial migration	3	0.0218	12.26	3.62
positive regulation of receptor-mediated endocytosis	2	0.0222	84.69	6.40
negative regulation of cholesterol efflux	2	0.0232	81.16	6.34
Ig_sub2	3	0.0235	11.91	3.57
identical protein binding	6	0.0258	3.25	1.70
Human papillomavirus infection	4	0.0267	5.70	2.51
regulation of synapse organization	2	0.0270	69.56	6.12
scavenger receptor activity	2	0.0273	68.76	6.10
negative regulation of smooth muscle cell proliferation	2	0.0279	67.17	6.07
cholesterol efflux	2	0.0289	64.93	6.02
endothelial cell proliferation	2	0.0298	62.83	5.97
vascular endothelial growth factor receptor signaling pathway	2	0.0298	62.83	5.97
extracellular matrix binding	2	0.0302	62.11	5.96
leukocyte cell-cell adhesion	2	0.0308	60.87	5.93
positive regulation of macroautophagy	2	0.0308	60.87	5.93
Apelin signaling pathway	3	0.0309	10.16	3.34
transmembrane receptor protein tyrosine kinase activity	2	0.0321	58.34	5.87
IGc2	3	0.0335	9.43	3.24
lysosome	3	0.0336	9.81	3.29
positive regulation of cell migration involved in sprouting angiogenesis	2	0.0336	55.65	5.80
Extracellular matrix	3	0.0351	9.57	3.26
triglyceride homeostasis	2	0.0355	52.64	5.72
Glycyl lysine isopeptide (Lys-Gly) (interchain with G-Cter in ubiquitin)	3	0.0355	9.51	3.25
negative regulation of gene expression	3	0.0361	9.42	3.24
membrane	10	0.0369	1.92	0.94
growth factor binding	2	0.0369	50.67	5.66
negative regulation of endothelial cell proliferation	2	0.0374	49.94	5.64
Phagosome	3	0.0391	8.95	3.16
Hepatitis C	3	0.0391	8.95	3.16
RTK	2	0.0394	47.29	5.56
Cyclin	2	0.0395	46.15	5.53
TRANSMEM:Helical	10	0.0397	1.90	0.92
response to nicotine	2	0.0402	46.38	5.54
Immune_injury_MS-lesions_genetic_environ	2	0.0408	38.80	5.28
KW-0675~Receptor	6	0.0425	2.70	1.43
peptidyl-tyrosine phosphorylation	2	0.0430	43.28	5.44
Ig-like_dom_sf	4	0.0431	4.77	2.25
positive regulation of nitric oxide biosynthetic process	2	0.0449	41.44	5.37
heterophilic cell-cell adhesion via plasma membrane cell adhesion molecules	2	0.0468	39.75	5.31
vascular endothelial growth factor receptor-1 signaling pathway	2	0.0468	39.75	5.31
platelet-derived growth factor receptor-alpha signaling pathway	2	0.0477	38.96	5.28

(*Contd.*)

Table S2 — Total gene ontology and pathway enrichment analysis.

Term	Count	P-Value	Fold Enrichment	Enrichment Log 2
epithelial cell proliferation	2	0.0486	38.19	5.26
Kit signaling pathway	2	0.0486	38.19	5.26
macrophage colony-stimulating factor signaling pathway	2	0.0486	38.19	5.26
macrophage colony-stimulating factor receptor activity	2	0.0492	37.75	5.24
insulin receptor activity	2	0.0492	37.75	5.24
GPI-linked ephrin receptor activity	2	0.0492	37.75	5.24
hepatocyte growth factor receptor activity	2	0.0492	37.75	5.24
stem cell factor receptor activity	2	0.0492	37.75	5.24
protein tyrosine kinase collagen receptor activity	2	0.0492	37.75	5.24
placental growth factor receptor activity	2	0.0492	37.75	5.24
boss receptor activity	2	0.0492	37.75	5.24
platelet-derived growth factor alpha-receptor activity	2	0.0492	37.75	5.24
brain-derived neurotrophic factor receptor activity	2	0.0492	37.75	5.24

Table S3 — Top 9 enriched terms in each category.

Term	Log2 transformed Enrichment	P-Value	Count	Class	Fold Enrichment
Extracellular space	2.962	3.83E-10	14	CC	7.80
Platelet alpha granule lumen	6.256	3.91E-07	5	CC	76.45
Extracellular exosome	2.476	7.40E-07	12	CC	5.57
Glycoprotein	1.411	7.78E-07	18	BP	2.66
Secreted	2.288	2.75E-06	12	CC	4.88
Protein N-linked glycosylation	1.710	1.40E-05	14	BP	3.27
Positive regulation of angiogenesis	4.918	1.58E-05	5	BP	30.25
Integrin binding	4.910	1.62E-05	5	MF	30.08
Immunoglobulin-like domain binding	6.180	1.87E-05	4	MF	72.54