Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplemental to: Fajgenbaum DC, Langan RA, Japp AS, et al. PI3K/Akt/mTOR is a Novel Therapeutic Target in IL-6 Blockade Refractory iMCD.

SUPPLEMENTAL APPENDIX

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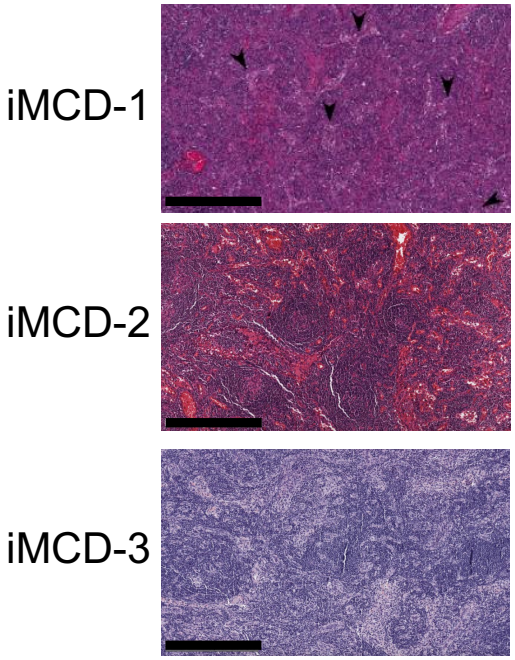

Fig S1. Hypervascularization of iMCD-1, iMCD-2, and iMCD-3 patient lymph nodes. High power representative images of hematoxylin and eosin stained lymph node excised from iMCD-1, iMCD-2, and iMCD-3. The lymph nodes demonstrate Castleman disease histopathology (atrophic, regressed germinal centers, increased interfollicular vascularity (arrows) and polytypic plasmacytosis) (bar = 500 um).

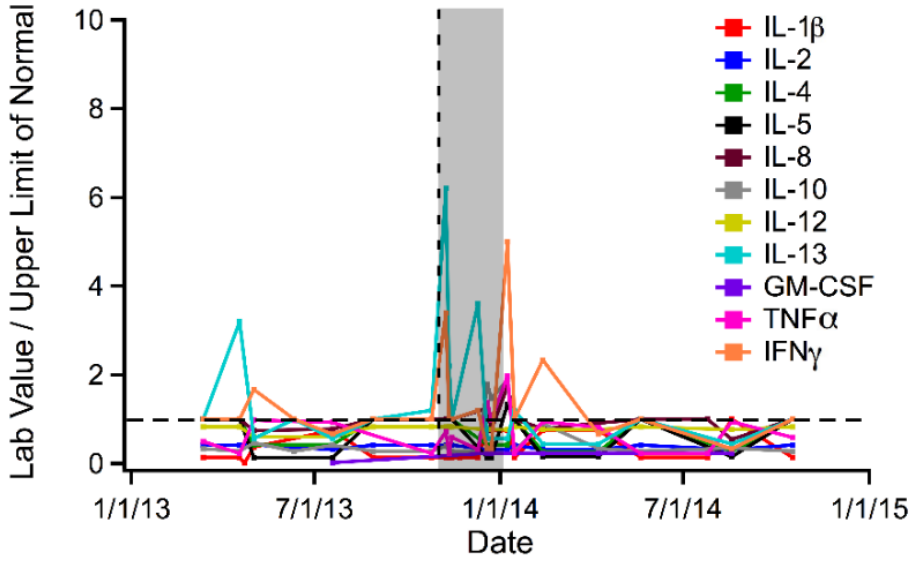

Fig. S2. Clinical laboratory values of serum inflammatory cytokines during the period leading up to, during, and after iMCD-1's fifth flare. Interleukin(IL)-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, IL-13, GM-CSF, TNFα and IFNγ test results normalized to the upper limits of normal for each laboratory test, measured over the time period leading up to and after the onset of iMCD-1's fifth disease flare. The onset of disease flare (defined by hypoalbuminemia (<3.5 g/dL), elevated C-Reactive Protein (>10 mg/L), anemia (hemoglobin <13.5 g/dL), renal dysfunction (creatinine >1.3 mg/dL), constitutional symptoms, and fluid accumulation), is indicated by the dotted vertical line and the duration is indicated by the shaded region. IL-6 levels become uninterpretable after siltuximab administration, so IL-6 is not included. sIL-2Rα, soluble interleukin-2 receptor alpha chain; VEGF-A, vascular endothelial growth factor A; GM-CSF, granulocyte-macrophage colony-stimulating factor; TNFα, tumor necrosis factor-alpha; IFNγ, interferon-gamma.

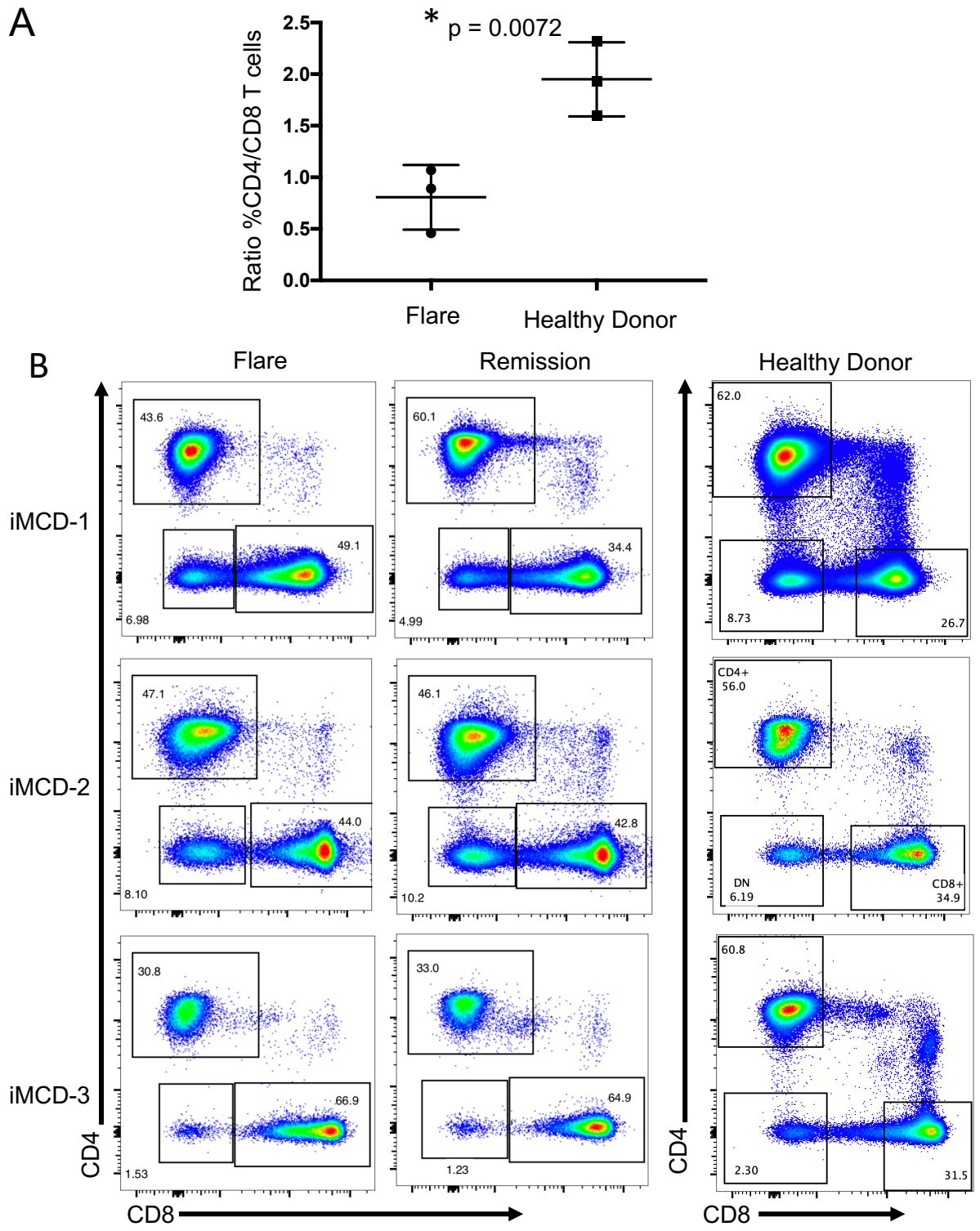

Fig. S3. CD4/CD8 T cell ratio is inverted. Flow cytometry of PBMCs obtained from iMCD-1, iMCD-2, and iMCD-3, gated for live $CD3^+$ T cells at onset of a relapse of Flare, Remission, and from age-matched healthy controls (Control). Unpaired one-sided t test was performed between the three iMCD flare samples and three age-matched healthy controls, alpha = 0.05.

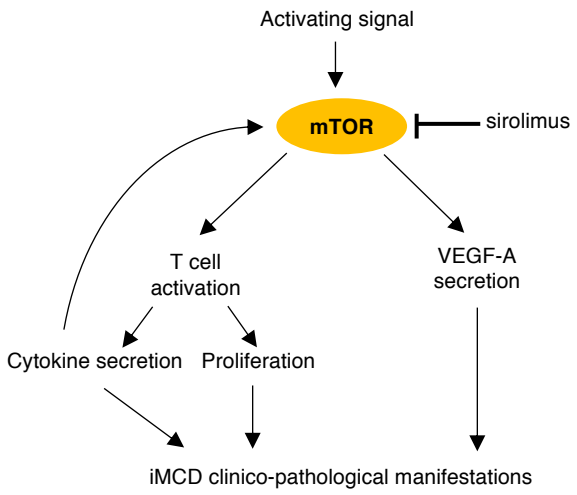

Fig. S4. Hypothesized model for the mechanism of sirolimus' efficacy. The data presented in this study suggest that mTOR is a central signaling pathway critical to T cell activation and VEGF-A secretion, which leads to iMCD clinical and pathological features. The activating signal is unknown.

Table S1. Myriad RBM DiscoveryMAP v.3.3 datasets for iMCD-1.

DiscoveryMAP		Flare 3	Flare 5
Protein	Abbreviated Name	Log_2Fold-change	Log_2Fold-change
C-Reactive Protein	CRP	4.91	4.74
Pancreatic secretory trypsin inhibitor	TATI	4.12	4.12
N-terminal prohormone of brain natriuretic peptide	NT pro-BNP	5.77	3.96
Serum Amyloid A Protein	SAA	3.39	3.90
Beta Amyloid 1-40	AB-40	4.45	3.67
Vascular Endothelial Growth Factor A	VEGF-A	3.36	3.67
Fibroblast Growth Factor 21	FGF-21	2.26	3.46
Tissue Inhibitor of Metalloproteinases 3	TIMP-3	3.38	3.13
Myeloid Progenitor Inhibitory Factor 1	MPIF-1	3.14	2.98
Adrenomedullin	ADM	3.02	2.80
Tenascin-C	TN-C	1.66	2.77
E-Selectin	-	2.37	2.57
Insulin-like Growth Factor Binding Protein 4	IGFBP4	2.40	2.54
Chitinase-3-like protein 1	YKL-40	2.53	2.36
Interleukin-2 receptor alpha	IL-2 receptor alpha	2.43	2.32
ST2	-	2.28	2.23
Fibroblast growth factor 23	FGF-23	2.61	2.06
Tissue Inhibitor of Metalloproteinases 1	TIMP-1	2.14	2.06
Macrophage inflammatory protein 3 beta	MIP-3 beta	2.52	2.02
Placenta Growth Factor	PLGF	1.21	1.97
Collagen IV	-	1.18	1.86
B Lymphocyte Chemoattractant	BLC	2.76	1.73
Pulmonary and Activation-Regulated Chemokine	PARC	2.98	1.57
Matrix Metalloproteinase-10	MMP-10	1.35	1.53
Osteopontin	-	1.74	1.53
Growth/differentiation factor 15	GDF-15	1.84	1.53
TNF-Related Apoptosis-Inducing Ligand Receptor 3	TRAIL-R3	1.66	1.49
Beta Amyloid 1-42	AB-42	1.44	1.48
Stem Cell Factor	SCF	1.13	1.27
Tumor Necrosis Factor Receptor I	TNF RI	1.44	1.27
6Ckine	-	1.54	1.25
Calbindin	-	1.29	1.25
Eotaxin-2	-	1.36	1.16
Vascular Cell Adhesion Molecule-1	VCAM-1	1.54	1.11
Alpha-1-acid glycoprotein 1	AGP-1	1.47	1.11

Human Epididymis Protein 4	HE4	1.85	1.09
Osteocalcin	-	1.06	1.08
Chemokine CC-4	HCC-4	1.09	1.06
Osteoprotegerin	OPG	1.05	1.05
Complement component C1q receptor	C1qR1	1.39	1.00
Lipocalin-1	LCN1	-2.94	-1.04
Erythropoietin	EPO	-1.08	-1.08
Apolipoprotein D	Apo D	-1.44	-1.09
Neuronal Cell Adhesion Molecule	N-CAM	-1.12	-1.12
Tumor necrosis factor ligand superfamily member 12	Tweak	-1.14	-1.14
Mesothelin	MSLN	-1.26	-1.17
Epidermal Growth Factor Receptor	EGFR	-1.08	-1.19
Apolipoprotein C-III	Apo C-III	-1.57	-1.20
Prostate Specific Antigen, total	tPSA	-3.83	-1.21
Clusterin	CLU	-1.14	-1.25
Dopamine beta-hydroxylase	DBH	-1.50	-1.26
Glucose-6-phosphate Isomerase	G6PI	-1.32	-1.27
Cancer Antigen 19-9	CA-19-9	-1.29	-1.29
Apolipoprotein C-I	Apo C-I	-1.06	-1.29
Protein S100A12	EN-RAGE	-1.58	-1.30
Interleukin-1 receptor antagonist	IL-1ra	-1.51	-1.33
Cystatin-A	-	-2.97	-1.38
Lactoferrin	LTF	-1.40	-1.45
Eotaxin-1	-	-2.30	-1.58
Epithelial-Derived Neutrophil-Activating Protein 78	ENA-78	-1.32	-1.61
Peroxiredoxin-4	Prx-IV	-1.34	-1.67
Epiregulin	EPR	-1.68	-1.68
Interleukin-7	IL-7	-1.71	-1.71
Interferon-inducible T-cell alpha chemoattractant	ITAC	-1.00	-1.72
Prostate-Specific Antigen, Free	PSA-f	-2.00	-2.00
Growth-Regulated alpha protein	GRO-alpha	-2.09	-2.09
Visfatin	-	-2.75	-2.10
Heparin-Binding EGF-Like Growth Factor	HB-EGF	-2.15	-2.15
Protein S100-A6	S100-A6	-1.10	-2.20
Myeloperoxidase	MPO	-2.74	-2.23
Thymus and activation-regulated chemokine	TARC	-1.42	-2.36
Lectin-Like Oxidized LDL Receptor 1	LOX-1	-2.51	-2.51
T-Cell-Specific Protein RANTES	RANTES	-1.24	-2.58
Aldose Reductase	-	-2.51	-2.87
Protein DJ-1	DJ-1	-1.66	-2.89

Macrophage Migration Inhibitory Factor	MIF	-1.05	-3.01
Epidermal Growth Factor	EGF	-2.61	-3.79
Macrophage Inflammatory Protein-3 alpha	MIP-3 alpha	-4.44	-4.00
Monocyte Chemotactic Protein 3	MCP-3	-4.01	-4.01
Tumor Necrosis Factor alpha	TNF-alpha	-4.21	-4.21
Insulin	-	-4.35	-4.35
Monocyte Chemotactic Protein 1	MCP-1	-4.54	-5.06
Interleukin-1 beta	IL-1 beta	-5.77	-5.53
Macrophage Inflammatory Protein-1 alpha	MIP-1 alpha	-5.17	-5.69
Macrophage Inflammatory Protein-1 beta	MIP-1 beta	-5.47	-6.10
Interleukin-8	IL-8	-11.25	-9.78

All proteins with a fold-change of ≥ 2 (e.g. absolute value log2(flare/remission ≥ 1) during both flares and in the same direction (e.g. increase or decrease) are presented.

Table S2. DiscoveryMAP gene set submitted to Enrichr to identify enriched gene sets from Kyoto Encyclopedia of Genes and Genomes (KEGG) and Library of Integrated Network-based Cell Signature (LINCS) 1000 for iMCD-1.

DiscoveryMAP		Flare 3	Flare 5
Protein	Submitted to Enrichr	Log_2Fold-change[A]	Log_2Fold-change[A]
APP_AB40	APP	5.32	4.54
NPPB	NPPB	5.77	3.96
CRP	CRP	4.91	4.74
GH1	GH1	4.28	
SAA1	SAA1	3.39	3.90
CXCL13	CXCL13	4.04	3.01
VEGF-A	VEGF-A	3.36	3.67
TIMP3	TIMP3	3.38	3.13
CCL23	CCL23	3.14	2.98
CCL18	CCL18	2.98	
PGR	PGR		2.96
ADM	ADM	3.02	2.80
FGF21	FGF21	2.26	3.46
TNC	TNC		2.77
FGF23	FGF23	2.97	2.42
CD27	CD27	2.67	
THBS4	THBS4	2.59	
SELE	SELE	2.37	2.57
IGFBP4	IGFBP4	2.40	2.54
CHI3L1	CHI3L1	2.53	2.36
MUC16	MUC16	2.38	
IL2RA	IL2RA	2.43	2.32
CCL19	CCL19	2.52	2.02
IL1RL1	IL1RL1	2.28	2.23
TIMP1	TIMP1	2.14	2.06
IL10	IL10	2.08	
CXCL1	CXCL1	-2.09	-2.09
TG	TG		-2.12
S100A6	S100A6		-2.20
CCL17	CCL17		-2.36
CCL22	CCL22		-2.37
KLK3_free	KLK3	-2.39	-2.39
NAMPT	NAMPT	-2.75	-2.10
NRCAM	NRCAM	-2.43	-2.43
MPO	MPO	-2.74	-2.23

CCL5	CCL5		-2.58
AKR1B1	AKR1B1	-2.51	-2.87
EREG	EREG	-2.72	-2.72
CSTA	CSTA	-2.73	
LEP	LEP	-2.74	
CA9	CA9	-2.82	-2.82
PARK7	PARK7		-2.89
CCL11	CCL11	-2.93	
LCN1	LCN1	-2.94	
MIF	MIF		-3.01
EGF	EGF	-2.61	-3.79
HBEGF	HBEGF	-3.21	-3.21
CEACAM6	CEACAM6	-3.27	
TNF	TNF	-3.32	-3.32
OLR1	OLR1	-3.36	-3.36
EPO	EPO	-3.97	-3.97
INS	INS	-4.42	-4.42
CCL2	CCL2	-4.54	-5.06
TNXB	TNXB	-4.83	
CCL20	CCL20	-5.77	-4.00
KLK3_total	KLK3	-5.08	
CCL3	CCL3	-5.17	-5.69
CCL7	CCL7	-5.73	-5.73
CCL4	CCL4	-5.47	-6.10
PSTI	PSTI	-6.15	-6.15
IL1B	IL1B	-7.29	-5.53

All proteins with a $\log_2$fold-change >2 for each of flare 3 and flare 5. Each set of proteins was submitted independently to Enrichr for comparisons to gene sets from KEGG and LINCS 1000.

[A](flare/remission)

Table S3. Results of Library of Integrated Network-based Cell Signature (LINCS) 1000 analyses of DiscoveryMAP datasets for iMCD-1.

	Flare 3		Flare 5		
Compound	Overlap[A]	Proteins[B]	Overlap[A]	Proteins[B]	Target (inhibition)
AZ-628	4/53	APP;SELE;THBS4;VEGFA	3/53	APP;SELE;VEGFA	Pan-Raf
I-BET	4/120	CD27;CCL18;SELE;VEGFA			Bromodomain
AS-605240	4/95	IGFBP4;CHI3L1;ADM;VEGFA	4/95	IGFBP4;CHI3L1;ADM;VEGFA	PI3K-gamma
ALW-II-38	3/39	CHI3L1;TIMP3;VEGFA	3/39	CHI3L1;TIMP3;VEGFA	Eph tyrosine kinase
GSK-1059615	3/45	MUC16;ADM;VEGFA			PI3K and mTOR
SB-525334	3/40	TIMP3;ADM;VEGFA	3/40	TIMP3;ADM;VEGFA	TGF-beta/SMAD
AZD-8330	3/40	CHI3L1;TIMP3;VEGFA	3/40	CHI3L1;TIMP3;VEGFA	MEK
JNK-9L			4/154	TNC;CHI3L1;ADM;VEGFA	JNK
GDC-0980			4/78	TNC;ADM;CXCL13;VEGFA	PI3K and mTOR
PD-0325901			3/79	TNC;TIMP3;VEGFA	MEK
GSK-1070916			3/41	TNC;CHI3L1;VEGFA	Aurora Kinase
BI-2536			3/83	TNC;CCL19;VEGFA	PLK
Sirolimus			3/55	TNC;CXCL13;VEGFA	mTOR
Pelitinib			3/81	TNC;ADM;VEGFA	EGFR
AZD-6482			3/42	TNC;CHI3L1;VEGFA	PI3K
WZ-3105			3/82	TNC;ADM;VEGFA	FLT3
CGP-60474			3/81	ADM;CCL19;VEGFA	CDK1/2

All compounds with FDR <0.01 and predicted to decrease VEGFA expression for flare 3 and flare 5. Compounds able to down-regulate sIL-2Rα were not identified. Table S5 presents the DiscoveryMAP gene sets for each flare used for enrichment analysis.

[A]Overlap of proteins identified to be up-regulated by DiscoveryMAP analysis and those known to be oppositely affected by the compound.

[B]Table S3 presents full names of all proteins.

Table S4. SomaLogic SOMAscan datasets for iMCD-1.

SOMAscan		Flare 3	Flare 5
Protein	Abbreviated Name	Log_2Fold-change	Log_2Fold-change
C-X-C Motif Chemokine Ligand 13	CXCL13	5.44	4.59
Complement C3	C3	5.49	2.60
Thrombospondin 2	THBS2	3.39	4.09
C-C Motif Chemokine Ligand 21	CCL21	3.47	3.68
Serum Amyloid A1	SAA1	3.02	3.62
Phospholipase A2 Group IIA	PLA2G2A	3.82	2.58
C-C Motif Chemokine Ligand 23	CCL23	3.08	3.07
Interleukin 1 Receptor Like 1	IL1RL1	3.03	3.09
Integrin Binding Sialoprotein	IBSP	2.11	4.01
Hepcidin Antimicrobial Peptide	HAMP	2.74	3.09
C-C Motif Chemokine Ligand 14	CCL14	2.71	2.55
Selectin E	SELE	2.52	2.74
Interleukin 1 Receptor Type 1	IL1R1	2.85	2.19
C-C Motif Chemokine Ligand 19	CCL19	2.47	2.54
Mannose Binding Lectin 2	MBL2	2.56	2.45
Milk Fat Globule-EGF Factor 8 Protein	MFGE8	2.02	2.89
Interleukin 18 Binding Protein	IL18BP	2.34	2.48
Slam Family Member 7	SLAMF7	2.78	2.04
Oxidized Low Density Lipoprotein Receptor 1	OLR1	3.53	1.24
C-Reactive Protein	CRP	2.14	2.48
TNF Alpha Induced Protein 6	TNFAIP6	2.11	2.47
Pappalysin 1	PAPPA	2.14	2.41
Matrix Metallopeptidase 13	MMP13	1.48	3.05
Vascular Endothelial Growth Factor A	VEGF-A	2.70	1.77
TNF Receptor Superfamily Member 6b	TNFRSF6B	2.04	2.42

Lipopolysaccharide Binding Protein	LBP	2.12	2.15
Tenascin C	TNC	1.87	2.36
Timp Metallopeptidase Inhibitor 1	TIMP1	2.07	2.16
Periostin	POSTN	2.19	1.89
Immunoglobulin Heavy Constant Epsilon	IGHE	1.83	2.21
Semaphorin 3e	SEMA3E	2.11	1.91
MHC Class I Polypeptide-Related Sequence A	MICA	1.98	1.97
Ephrin A4	EFNA4	2.09	1.80
C-C Motif Chemokine Ligand 25	CCL25	1.94	1.95
Cd274 Molecule	CD274	1.42	2.43
Protease, Serine 2	PRSS2	2.24	1.61
Angiopoietin 2	ANGPT2	1.93	1.92
Fibroblast Growth Factor 19	FGF19	1.72	2.13
Relt, TNF Receptor	RELT	1.94	1.85
GDNF Family Receptor Alpha 1	GFRA1	1.91	1.88
Agouti Related Neuropeptide	AGRP	1.64	2.14
Leukocyte Immunoglobulin Like Receptor B2	LILRB2	1.32	2.43
Wnt Inhibitory Factor 1	WIF1	1.65	1.90
Glycoprotein Hormones, Alpha Polypeptide	CGA	2.52	1.00
Lipocalin 2	LCN2	1.98	1.54
Carbohydrate Sulfotransferase 15	CHST15	1.59	1.89
Midkine (Neurite Growth-Promoting Factor 2)	MDK	1.30	2.12
C-X-C Motif Chemokine Ligand 12	CXCL12	1.48	1.92
Hepatitis A Virus Cellular Receptor 2	HAVCR2	1.71	1.66
Beta-2-Microglobulin	B2M	1.88	1.48
Glutathione S-Transferase Alpha 3	GSTA3		3.29
Ephrin A5	EFNA5	1.67	1.62
Neuroligin 4, X-Linked	NLGN4X	1.58	1.69
Pancreatic Polypeptide	PPY	1.28	1.98
Eph Receptor B2	EPHB2	2.02	1.23

Matrix Metallopeptidase 12	MMP12		3.23
Resistin	RETN	1.36	1.87
Bone Marrow Stromal Cell Antigen 1	BST1	1.67	1.51
Eph Receptor A2	EPHA2	1.74	1.39
Plasminogen Activator, Urokinase Receptor	PLAUR	1.70	1.33
Interleukin 18 Receptor 1	IL18R1	1.88	1.14
Coiled-Coil Domain Containing 80	CCDC80	1.69	1.32
Cystatin F	CST7	1.42	1.58
Thymidylate Synthetase	TYMS	1.67	1.28
Trefoil Factor 3	TFF3	1.59	1.35
TNF Receptor Superfamily Member 19	TNFRSF19	1.62	1.30
BOC Cell Adhesion Associated, Oncogene Regulated	BOC	1.58	1.30
Matrix Metallopeptidase 9	MMP9	2.81	
Insulin Like Growth Factor Binding Protein 2	IGFBP2	1.27	1.48
TNF Receptor Superfamily Member 1a	TNFRSF1A	1.32	1.41
Fc Fragment Of Igg Receptor IIA	FCGR2A	1.39	1.33
Interleukin 10	IL10		2.71
Insulin Like Growth Factor Binding Protein 7	IGFBP7	1.14	1.57
Stanniocalcin 1	STC1	1.31	1.39
Cystatin Sa	CST2	1.26	1.43
Cystatin D	CST5	1.03	1.63
C-C Motif Chemokine Ligand 18	CCL18	1.59	1.06
C-C Motif Chemokine Ligand 15	CCL15	1.15	1.43
Adam Metallopeptidase Domain 9	ADAM9	1.36	1.20
Plasminogen Activator, Urokinase	PLAU	1.30	1.25
Placental Growth Factor	PGF		2.54
Follistatin Like 3	FSTL3	1.17	1.37
C-C Motif Chemokine Ligand 3	CCL3	1.41	1.12
Apolipoprotein B	APOB	1.47	1.06
Cd300c Molecule	CD300C	1.08	1.44

Inhibin Beta A Subunit	INHBA	1.02	1.47
Transglutaminase 3	TGM3		2.48
Interleukin 13 Receptor Subunit Alpha 1	IL13RA1	1.35	1.12
Cd33 Molecule	CD33	1.17	1.29
C-X-C Motif Chemokine Ligand 6	CXCL6	1.10	1.35
Endoglin	ENG	1.01	1.43
Matrix Metallopeptidase 3	MMP3	1.13	1.31
TNF Receptor Superfamily Member 17	TNFRSF17	1.42	1.01
Protease, Serine 22	PRSS22	1.34	1.08
Cerebral Dopamine Neurotrophic Factor	CDNF	1.40	1.01
Sialic Acid Binding Ig Like Lectin 14	SIGLEC14	1.12	1.27
Cystatin C	CST3	1.37	1.02
MHC Class I Polypeptide-Related Sequence B	MICB	1.05	1.34
TNF Receptor Superfamily Member 1b	TNFRSF1B	1.01	1.33
Cathepsin H	CTSH	1.28	1.06
Netrin 4	NTN4	1.00	1.27
Cytotoxic T-Lymphocyte Associated Protein 4	CTLA4	1.20	1.06
Interleukin 17 Receptor C	IL17RC	1.07	1.14
Renin	REN		2.18
Interleukin 4 Receptor	IL4R	1.01	1.16
Protein Kinase C Gamma	PRKCG	2.14	
TEK Receptor Tyrosine Kinase	TEK	1.09	1.04
Neurexophilin 1	NXPH1	2.12	
Vascular Cell Adhesion Molecule 1	VCAM1	1.00	1.07
Peptide YY	PYY	1.03	1.02
Granulysin	GNLY		2.02
Lactotransferrin	LTF	1.94	
Ectodysplasin A2 Receptor	EDA2R		1.92
Troponin I2, Fast Skeletal Type	TNNI2		1.80
Glucagon	GCG		1.78

Lymphocyte Activating 3	LAG3	1.74	
Insulin Like Growth Factor Binding Protein 1	IGFBP1	1.73	
Fibroblast Growth Factor 23	FGF23		1.66
Alkaline Phosphatase, Liver/Bone/Kidney	ALPL	1.65	
Granzyme A	GZMA	1.63	
Glycoprotein IB Platelet Alpha Subunit	GP1BA		1.61
Cathepsin B	CTSB	1.59	
Cyclin Dependent Kinase Inhibitor 1b	CDKN1B		1.50
Natural Cytotoxicity Triggering Receptor 1	NCR1		1.48
C-X-C Motif Chemokine Ligand 11	CXCL11	1.46	
Ectonucleotide Pyrophosphatase/Phosphodiesterase 7	ENPP7	1.45	
Interleukin 5 Receptor Subunit Alpha	IL5RA	1.41	
Fucosyltransferase 5	FUT5	1.38	
C-C Motif Chemokine Ligand 7	CCL7		1.37
Carbonic Anhydrase 2	CA2		1.36
Cystatin E/M	CST6		1.35
Cd86 Molecule	CD86		1.33
Insulin Receptor	INSR		1.33
Leukocyte Immunoglobulin Like Receptor B1	LILRB1		1.33
Spondin 1	SPON1	1.32	
Leucine Rich Repeats And Immunoglobulin Like Domains 3	LRIG3	1.26	
Cytochrome P450 Oxidoreductase	POR	1.26	
Glypican 3	GPC3		1.26
C-C Motif Chemokine Ligand 16	CCL16	1.25	
Scavenger Receptor Class F Member 2	SCARF2		1.24
Peptidase Inhibitor 3	PI3		1.23
Matrix Metallopeptidase 7	MMP7	1.21	
Chitinase 1	CHIT1		1.18
Dead-Box Helicase 19b	DDX19B		1.17
Cathepsin Z	CTSZ		1.17

Interleukin 11 Receptor Subunit Alpha	IL11RA	1.13	
Proteinase 3	PRTN3		1.12
Serpin Family A Member 3	SERPINA3	1.11	
Protease, Serine 1	PRSS1	1.09	
TNF Receptor Superfamily Member 18	TNFRSF18	1.08	
Lymphocyte Antigen 9	LY9	1.08	
Toll Like Receptor 4	TLR4	1.07	
Complement Factor D	CFD	1.07	
Platelet Derived Growth Factor C	PDGFC		1.07
Collagen Type Viii Alpha 1 Chain	COL8A1		1.07
C-X-C Motif Chemokine Ligand 16	CXCL16		1.06
Mitogen-Activated Protein Kinase 9	MAPK9	1.06	
Retinoic Acid Receptor Responder 2	RARRES2	1.06	
Mannose Receptor C-Type 1	MRC1		1.05
Interleukin 22 Receptor Subunit Alpha 2	IL22RA2	1.05	
Collagen Type Xviii Alpha 1 Chain	COL18A1		1.04
C-Type Lectin Domain Containing 11a	CLEC11A		1.04
Chordin Like 1	CHRDL1		1.04
Endothelial Cell Specific Molecule 1	ESM1		1.03
Fatty Acid Binding Protein 3	FABP3	1.03	
Unc-5 Netrin Receptor C	UNC5C		1.03
Insulin Like Growth Factor 1 Receptor	IGF1R	1.02	
Endothelial Cell Adhesion Molecule	ESAM		1.02
Diablo IAP-Binding Mitochondrial Protein	DIABLO		1.01
Fatty Acid Binding Protein 5	FABP5		1.01
Thrombospondin 4	THBS4	1.01	
Colony Stimulating Factor 2	CSF2	1.00	
Bone Morphogenetic Protein 7	BMP7		1.00
Kras Proto-Oncogene, GTPase	KRAS		1.00
Fc Fragment Of IGE Receptor II	FCER2	-1.42	1.66

Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Gamma	PIK3CG		-1.02
Ephrin B3	EFNB3	-1.03	
Retinol Binding Protein 4	RBP4		-1.04
Fibroblast Growth Factor 6	FGF6		-1.04
Interleukin 3 Receptor Subunit Alpha	IL3RA		-1.06
At-Rich Interaction Domain 3a	ARID3A		-1.06
Aldo-Keto Reductase Family 1 Member A1	AKR1A1		-1.07
Angiopoietin 1	ANGPT1		-1.08
Interleukin 22 Receptor Subunit Alpha 1	IL22RA1	-1.10	
Fibroblast Growth Factor 8	FGF8		-1.11
Ul16 Binding Protein 3	ULBP3		-1.11
FMS Related Tyrosine Kinase 3	FLT3		-1.13
Calcium/Calmodulin Dependent Protein Kinase Ii Alpha	CAMK2A		-1.13
Cytokine Receptor-Like Factor 2	CRLF2		-1.14
NME/NM23 Nucleoside Diphosphate Kinase 1	NME1	-1.14	
Ribosomal Protein S27a	RPS27A		-1.14
GDNF Family Receptor Alpha 3	GFRA3	-1.15	
C-C Motif Chemokine Ligand 22	CCL22		-1.17
Legumain	LGMN	-1.17	
Protein Tyrosine Phosphatase, Non-Receptor Type 11	PTPN11		-1.18
Cathepsin G	CTSG	-1.21	
Connective Tissue Growth Factor	CTGF		-1.21
Proteasome Subunit Alpha 2	PSMA2		-1.21
Amyloid Beta Precursor Protein	APP		-1.22
Ectodysplasin A Receptor	EDAR		-1.23
SHC Adaptor Protein 1	SHC1		-1.23
Complement Factor H Related 5	CFHR5		-1.24
Lactate Dehydrogenase B	LDHB		-1.24
Ubiquitin-Fold Modifier Conjugating Enzyme 1	UFC1		-1.25

Azurocidin 1	AZU1		-1.25
Junctional Adhesion Molecule 3	JAM3		-1.25
Catalase	CAT		-1.26
Inducible T-Cell Costimulator Ligand	ICOSLG	-1.29	
Activin A Receptor Type 1b	ACVR1B	-1.29	
Ferritin Heavy Chain 1	FTH1		-1.29
Dual Specificity Phosphatase 3	DUSP3		-1.30
Glycoprotein Vi Platelet	GP6	-1.30	
Interleukin 23 Receptor	IL23R		-1.34
Kallikrein Related Peptidase 14	KLK14		-1.34
Phosphatidylethanolamine Binding Protein 1	PEBP1		-1.38
Fibronectin Leucine Rich Transmembrane Protein 1	FLRT1		-1.40
Desert Hedgehog	DHH		-1.40
Complement Factor Properdin	CFP	-1.49	
Seizure Related 6 Homolog Like 2	SEZ6L2		-1.50
Peroxiredoxin 6	PRDX6		-1.54
Ribosomal Protein S6 Kinase A5	RPS6KA5		-1.54
Zeta Chain Of T-Cell Receptor Associated Protein Kinase 70	ZAP70		-1.54
Euchromatic Histone Lysine Methyltransferase 2	EHMT2		-1.56
Proteasome Subunit Alpha 6	PSMA6		-1.61
GDP Dissociation Inhibitor 2	GDI2		-1.69
Synaptotagmin Binding Cytoplasmic RNA Interacting Protein	SYNCRIP		-1.75
Stress Induced Phosphoprotein 1	STIP1		-1.76
Karyopherin Subunit Beta 1	KPNB1		-1.76
Eukaryotic Translation Initiation Factor 5a	EIF5A		-1.77
Acid Phosphatase 1, Soluble	ACP1		-1.77
Protein Kinase C Iota	PRKCI		-1.78
Mitogen-Activated Protein Kinase 3	MAPK3		-1.86
Bcl2, Apoptosis Regulator	BCL2		-1.90
Interferon Gamma	IFNG		-1.90

Eukaryotic Translation Elongation Factor 1 Beta 2	EEF1B2		-1.90
Adenylate Kinase 1	AK1		-1.91
Immunoglobulin Heavy Constant Delta	IGHD	-1.91	
Glycogen Synthase Kinase 3 Alpha	GSK3A		-1.92
Malate Dehydrogenase 1	MDH1		-1.93
Ran, Member Ras Oncogene Family	RAN		-2.07
Transforming Growth Factor Beta 1	TGFB1	-1.05	-1.04
Ubiquitin Conjugating Enzyme E2 L3	UBE2L3		-2.09
Phosphodiesterase 11a	PDE11A	-1.08	-1.03
Serpin Family E Member 1	SERPINE1	-1.02	-1.09
Sh2 Domain Containing 1a	SH2D1A	-1.13	-1.01
Fibroblast Growth Factor 16	FGF16		-2.14
RNA Binding Motif Protein 39	RBM39	-1.02	-1.16
Peroxiredoxin 1	PRDX1		-2.20
Kringle Containing Transmembrane Protein 2	KREMEN2	-1.05	-1.16
Tumor Protein, Translationally-Controlled 1	TPT1		-2.22
C-C Motif Chemokine Ligand 13	CCL13	-1.12	-1.10
Platelet Derived Growth Factor Subunit A	PDGFA		-2.23
Interleukin 16	IL16	-1.11	-1.16
Proteasome Activator Subunit 1	PSME1	-1.03	-1.25
Erythrocyte Membrane Protein Band 4.1	EPB41		-2.31
Mitogen-Activated Protein Kinase Kinase Kinase 7	MAP3K7	-1.15	-1.16
N-Myristoyltransferase 1	NMT1	-1.10	-1.24
Protein Kinase Camp-Activated Catalytic Subunit Alpha	PRKACA	-1.00	-1.37
Amphiregulin	AREG		-2.37
Interleukin 2 Receptor Subunit Gamma	IL2RG		-2.39
Histone Acetyltransferase 1	HAT1	-1.11	-1.32
Peptidylprolyl Isomerase A	PPIA	-1.05	-1.42
Epidermal Growth Factor Receptor Pathway Substrate 15 Like 1	EPS15L1	-1.14	-1.34
Brain Derived Neurotrophic Factor	BDNF	-1.26	-1.25

Casein Kinase 2 Alpha 1	CSNK2A1		-2.53
Pyridoxal Phosphatase	PDXP		-2.58
Membrane Frizzled-Related Protein	MFRP	-1.30	-1.29
Phosphoglycerate Kinase 1	PGK1	-1.28	-1.31
Gremlin 1, Dan Family Bmp Antagonist	GREM1	-1.17	-1.47
Wnt1 Inducible Signaling Pathway Protein 1	WISP1	-1.41	-1.26
Ribosomal Protein S6 Kinase A3	RPS6KA3	-1.09	-1.58
Tata-Box Binding Protein	TBP	-1.62	-1.06
Sparc/Osteonectin, Cwcv And Kazal Like Domains Proteoglycan 1	SPOCK1	-1.22	-1.48
Inosine Monophosphate Dehydrogenase 2	IMPDH2	-1.37	-1.34
Moesin	MSN	-1.30	-1.43
Elastase, Neutrophil Expressed	ELANE	-1.58	-1.17
Mitogen-Activated Protein Kinase 8	MAPK8	-1.47	-1.28
Tyrosine Kinase 2	TYK2	-1.58	-1.18
Camp Regulated Phosphoprotein 19	ARPP19	-1.11	-1.70
Thrombospondin 1	THBS1	-1.21	-1.63
Cytochrome P450 Family 3 Subfamily A Member 4	CYP3A4	-1.48	-1.40
Apolipoprotein D	APOD	-1.31	-1.57
Annexin A2	ANXA2	-1.41	-1.49
Sirtuin 2	SIRT2	-1.50	-1.40
Secreted Protein Acidic And Cysteine Rich	SPARC	-1.55	-1.35
Carbonic Anhydrase 13	CA13	-1.16	-1.75
Collagen Type Xxiii Alpha 1 Chain	COL23A1	-1.22	-1.77
Cadherin 12	CDH12	-1.38	-1.62
Heat Shock Protein 90 Alpha Family Class A Member 1	HSP90AA1	-1.37	-1.64
Superoxide Dismutase 1	SOD1	-1.10	-1.93
Heat Shock Protein Family D (Hsp60) Member 1	HSPD1	-1.50	-1.56
Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Beta	YWHAB	-1.35	-1.73
Cadherin 6	CDH6	-1.72	-1.38

Protein Disulfide Isomerase Family A Member 3	PDIA3	-1.52	-1.58
Eph Receptor B4	EPHB4	-1.64	-1.49
Structure Specific Recognition Protein 1	SSRP1	-1.70	-1.48
Protein Kinase C Zeta	PRKCZ	-1.65	-1.54
Calcium/Calmodulin Dependent Protein Kinase Kinase 1	CAMKK1	-1.32	-1.88
C-X-C Motif Chemokine Ligand 3	CXCL3	-1.14	-2.07
Serine/Threonine Kinase 17b	STK17B	-1.50	-1.71
Carnosine Dipeptidase 1	CNDP1	-1.82	-1.39
Pyruvate Dehydrogenase Kinase 1	PDK1	-2.05	-1.20
Phosphogluconate Dehydrogenase	PGD	-1.26	-2.00
Creatine Kinase, M-Type	CKM	-2.22	-1.05
Protein Kinase C Theta	PRKCQ	-1.56	-1.73
Mitogen-Activated Protein Kinase 14	MAPK14	-1.77	-1.55
Allograft Inflammatory Factor 1	AIF1	-1.69	-1.62
Protein Phosphatase 3 Regulatory Subunit B, Alpha	PPP3R1	-1.60	-1.76
Dickkopf Like Acrosomal Protein 1	DKKL1	-1.81	-1.58
Calpain 1	CAPN1	-1.53	-1.87
Integrin Subunit Alpha 1	ITGA1	-1.17	-2.32
Sorting Nexin 4	SNX4	-1.05	-2.46
Peptidylprolyl Isomerase F	PPIF	-1.59	-1.91
Eukaryotic Translation Initiation Factor 4 Gamma 2	EIF4G2	-1.43	-2.08
Mitogen-Activated Protein Kinase 1	MAPK1	-1.17	-2.34
Protein Tyrosine Phosphatase, Non-Receptor Type 1	PTPN1	-1.69	-1.87
SBDS, Ribosome Maturation Factor	SBDS	-1.21	-2.35
G Protein-Coupled Receptor Kinase 2	GRK2	-1.55	-2.04
Inhibitor Of Growth Family Member 1	ING1	-1.40	-2.22
Protein Phosphatase 3 Catalytic Subunit Alpha	PPP3CA	-1.78	-1.84
Matrix Metallopeptidase 17	MMP17	-1.72	-1.90
Microtubule Associated Protein Tau	MAPT	-1.82	-1.84
Inosine Monophosphate Dehydrogenase 1	IMPDH1	-1.54	-2.14

Serpin Family E Member 2	SERPINE2	-1.78	-1.91
Calcium/Calmodulin Dependent Protein Kinase Ii Beta	CAMK2B	-1.39	-2.30
NME/NM23 Nucleoside Diphosphate Kinase 2	NME2	-1.22	-2.52
Transketolase	TKT	-1.30	-2.45
Ubiquitin Conjugating Enzyme E2 N	UBE2N	-1.17	-2.60
Sphingomyelin Phosphodiesterase Acid Like 3a	SMPDL3A	-2.12	-1.70
NSF Attachment Protein Alpha	NAPA	-1.32	-2.54
Mitogen-Activated Protein Kinase-Activated Protein Kinase 3	MAPKAPK3	-1.91	-1.95
Integrin Subunit Alpha 2b	ITGA2B	-1.48	-2.39
Triosephosphate Isomerase 1	TPI1	-1.44	-2.48
Ribosomal Protein S7	RPS7	-1.96	-1.96
Protein Tyrosine Phosphatase, Non-Receptor Type 6	PTPN6	-1.38	-2.57
ATP Synthase, H+ Transporting, Mitochondrial F1 Complex, Beta Polypeptide	ATP5B	-1.95	-2.01
Vesicle Trafficking 1	VTA1	-1.18	-2.81
Phosphodiesterase 2a	PDE2A	-1.99	-2.05
Cofilin 1	CFL1	-1.49	-2.56
Prostaglandin-Endoperoxide Synthase 2	PTGS2	-2.07	-2.12
Glyceraldehyde-3-Phosphate Dehydrogenase	GAPDH	-1.59	-2.61
Mitogen-Activated Protein Kinase-Activated Protein Kinase 2	MAPKAPK2	-1.92	-2.29
Akt Serine/Threonine Kinase 1	AKT1	-1.98	-2.34
Lyn Proto-Oncogene, Src Family Tyrosine Kinase	LYN	-1.73	-2.61
Creatine Kinase B	CKB	-3.04	-1.29
Protein Kinase Amp-Activated Catalytic Subunit Alpha 2	PRKAA2	-1.88	-2.47
Copine 1	CPNE1	-1.61	-2.78
Basigin (Ok Blood Group)	BSG	-2.37	-2.09
Protein Kinase C Alpha	PRKCA	-1.80	-2.69
Proliferation-Associated 2g4	PA2G4	-1.58	-2.95
P21 (Rac1) Activated Kinase 6	PAK6	-2.17	-2.39
Calcium/Calmodulin Dependent Protein Kinase Ii Delta	CAMK2D	-1.68	-2.91

Ras-Related C3 Botulinum Toxin Substrate 1 (Rho Family, Small GTP Binding Protein Rac1)	RAC1	-1.87	-2.75
Carbonic Anhydrase 6	CA6	-2.13	-2.50
Ubiquitin Conjugating Enzyme E2 I	UBE2I	-1.98	-2.70
Tec Protein Tyrosine Kinase	TEC	-2.18	-2.61
Hydroxysteroid 17-Beta Dehydrogenase 10	HSD17B10	-2.08	-2.77
FER Tyrosine Kinase	FER	-2.05	-2.85
Pyruvate Kinase, Muscle	PKM	-2.34	-2.65
Chymase 1	CMA1	-2.30	-2.73
Methionyl Aminopeptidase 1	METAP1	-2.05	-3.09
3-Phosphoinositide Dependent Protein Kinase 1	PDPK1	-2.07	-3.09
Sphingosine Kinase 1	SPHK1	-1.87	-3.32
Src Proto-Oncogene, Non-Receptor Tyrosine Kinase	SRC	-2.07	-3.18
Aldo-Keto Reductase Family 7 Member A2	AKR7A2	-1.91	-3.39
Peptidylprolyl Isomerase D	PPID	-2.17	-3.14
Chloride Intracellular Channel 1	CLIC1	-2.51	-2.83
Pro-Platelet Basic Protein	PPBP	-2.23	-3.13
Ribosomal Protein S3	RPS3	-2.64	-2.82
H2a Histone Family Member Z	H2AFZ	-3.26	-2.21
Annexin A6	ANXA6	-2.34	-3.30
Fyn Proto-Oncogene, Src Family Tyrosine Kinase	FYN	-2.52	-3.23
Heterogeneous Nuclear Ribonucleoprotein A/B	HNRNPAB	-2.66	-3.16
Protein Kinase C Beta	PRKCB	-2.74	-3.43
Bruton Tyrosine Kinase	BTK	-2.81	-3.37
CSK, Non-Receptor Tyrosine Kinase	CSK	-2.75	-3.55
Platelet Derived Growth Factor Subunit B	PDGFB	-2.43	-4.58
Topoisomerase (DNA) I	TOP1	-3.38	-3.67
Platelet Factor 4	PF4	-2.69	-4.36
Heterogeneous Nuclear Ribonucleoprotein A2/B1	HNRNPA2B1	-3.37	-3.81
High Mobility Group Box 1	HMGB1	-3.21	-4.26

Histone Cluster 1 H1 Family Member C	HIST1H1C	-3.97	-4.62
C-C Motif Chemokine Ligand 5	CCL5	-4.25	-5.64
Surfactant Protein D	SFTPD	-4.58	-5.63

All proteins with a fold-change of ≥2 (e.g. absolute value $\log_2$(flare/remission ≥1) for each of flare 3 and flare 5. Each set of proteins was analyzed independently using Ingenuity Pathway Analysis.

Table S5. Results of Ingenuity Pathway Analyses (IPA) of SOMAscan datasets for iMCD-1.

IPA of SOMAscan Flare 3		
Top five canonical pathways		-log(p-value)
1	PI3K Signaling in B Lymphocytes	5.26
2	mTOR Signaling	4.64
3	Protein Kinase A Signaling	4.64
4	Synaptic Long Term Potentiation	4.15
5	G Beta Gamma Signaling	4.15

IPA of SOMAscan Flare 5		
Top canonical pathways		-log(p-value)
1	PI3K Signaling in B Lymphocytes	3.82
2	Dopamine-DARPP32 Feedback in cAMP Signaling	3.38
3	Synaptic Long Term Potentiation	2.94
4	Agranulocyte Adhesion and Diapedesis	2.88
5	nNOS Signaling in Neurons	2.85
6-36	--	--
37	mTOR Signaling	1.48