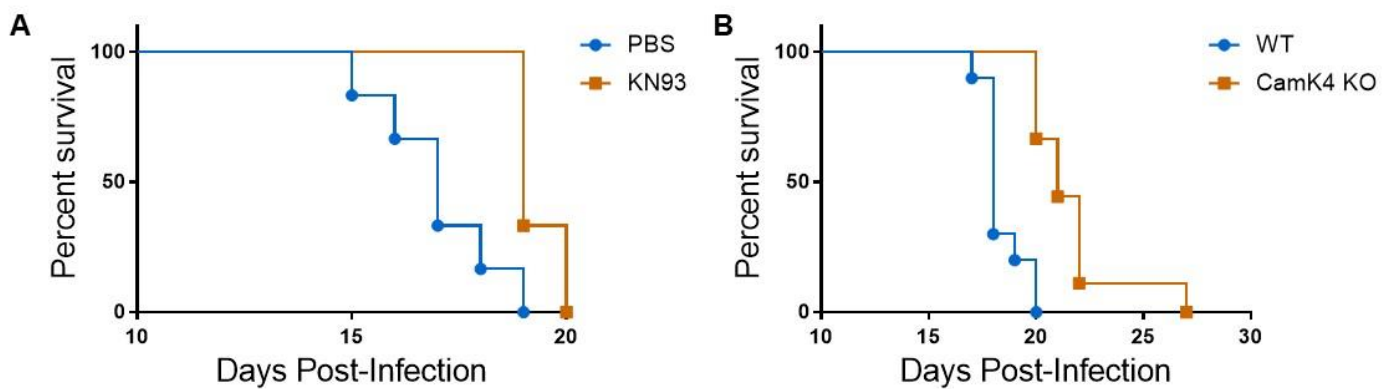
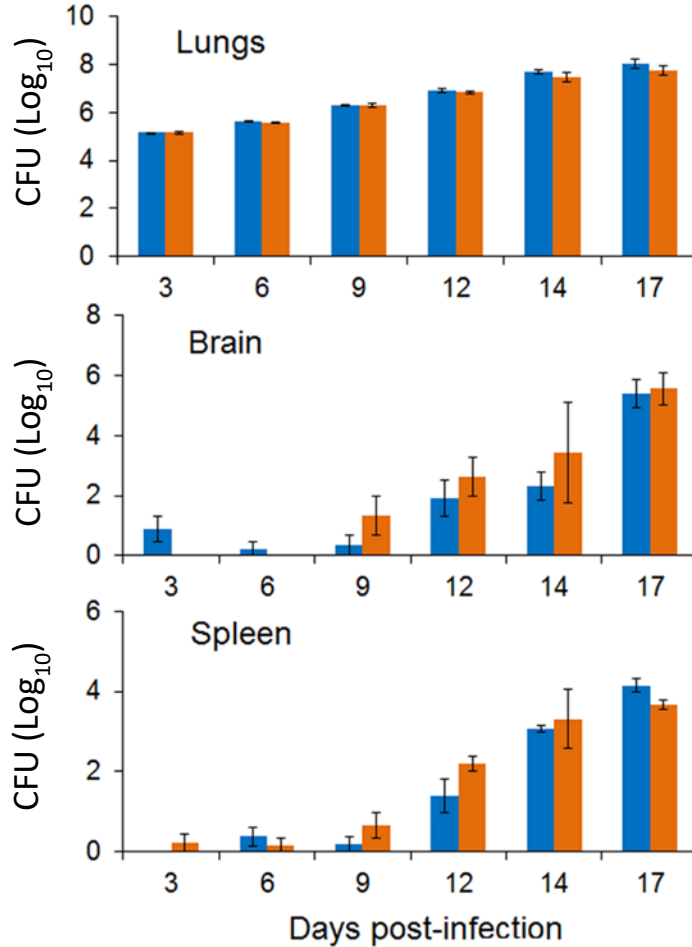


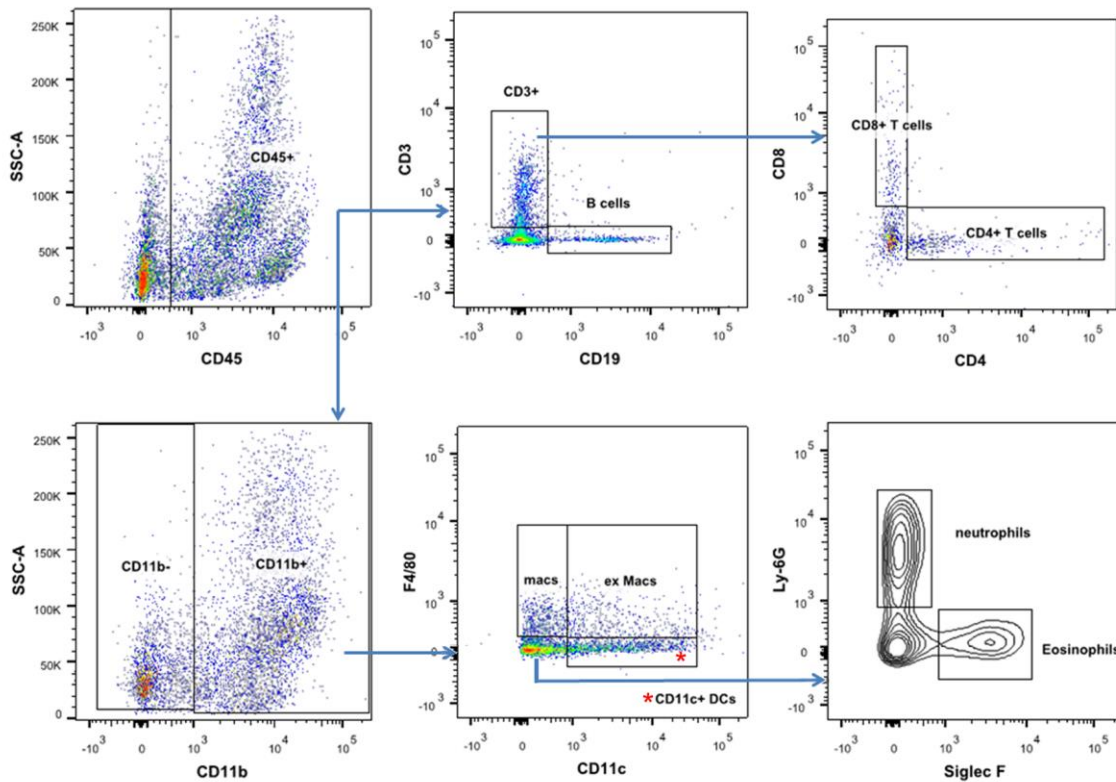
**Supplemental Figure 1. siRNA silencing efficiency.** THP-1 cells were differentiated and treated with no siRNA, control scrambled siRNA, or siRNA targeting the indicated proteins as described in the Materials and Methods section. At 48 h after transfection RNA was extracted and converted to cDNA and RT-PCR was performed to assess silencing efficiency for a randomly selected group of targets. Overall silencing ranged from 27% to 95%, with a mean of 66% and SEM of 5.8%. Data shown (mean ± SEM) are compiled from 3 technical and 2 biological replicates.



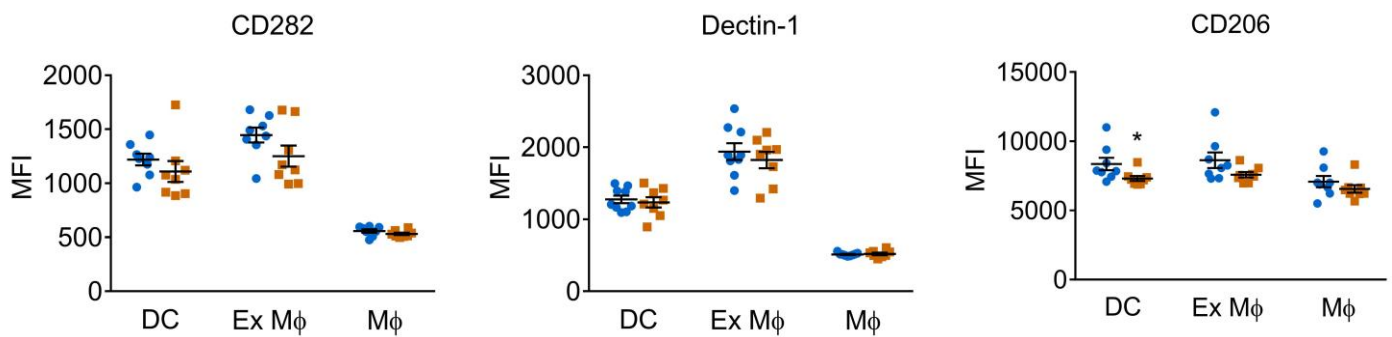
**Supplemental Figure 2. Additional mouse survival studies.** A. Survival of C57BL/6 mice treated with either PBS alone (blue) or with 250  $\mu\text{g/g}$  body weight KN93 in PBS (orange). Mice were treated one day prior to infection with  $5 \times 10^4$  cryptococci and three times a week post-infection. Results are from one experiment with 6 mice per group;  $p < 0.05$  by LogRank test. D. Wild type (WT;  $n=10$ ) and CaMK4 knockout mice ( $n=9$ ) were infected with *C. neoformans* and monitored as detailed in the Methods. Results are from one experiment;  $p < 0.05$  by LogRank test.



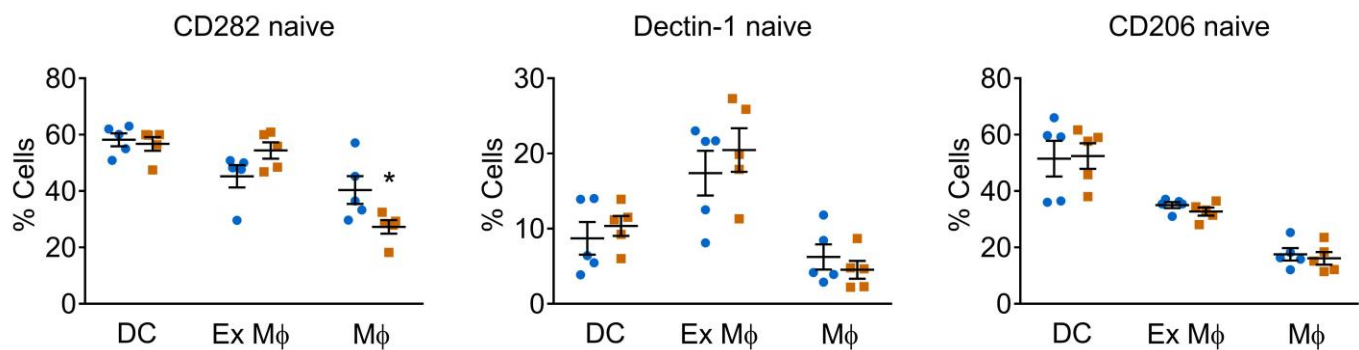
**Supplemental Figure 3. Absence of CamK4 does not influence organ burden of *C. neoformans*.** Lung, brain, and spleen were harvested from WT (blue) and CaMK4<sup>-/-</sup> (orange) mice at the indicated times after intranasal infection with  $5 \times 10^4$  cryptococci, and fungal burden was assessed by colony forming units (CFU). Data are from 2 independent experiments with 6-10 mice per group per time point; means  $\pm$  SEM are plotted.



**Supplemental Figure 4. Flow cytometry gating strategy.** Flow cytometry analysis of host leukocyte populations in WT mice 7 days after intranasal infection with  $10^4$  *C. neoformans*. After separation based on physical properties to eliminate debris and aggregated cells, dead cells were excluded by live/dead staining (not shown). CD45+ cells (leukocytes; top left) were subjected to analysis based on their expression of CD3, CD19, CD4, CD8, CD11b, CD11c, F4/80, Ly-6G, and Siglec F. The specific populations of cells identified are indicated on the flow plots.



**Supplemental Figure 5. Mean fluorescence intensity of PRRs.** PRR profiling of leukocytes from WT (blue circles) and CaMK4 knockout (orange squares) mice 7 days after infection with  $10^4$  *C. neoformans* KN99 $\alpha$ . Antibody labeling and flow cytometry were used to classify pulmonary leukocytes as DCs (CD45<sup>+</sup>, CD11b<sup>+</sup>, CD11c<sup>+</sup>, F4/80<sup>-</sup>), exudate or recruited macrophages (CD45<sup>+</sup>, CD11b<sup>+</sup>, CD11c<sup>+</sup>, F4/80<sup>+</sup>), or macrophages/monocytes (CD45<sup>+</sup>, CD11b<sup>+</sup>, CD11c<sup>-</sup>, F4/80<sup>+</sup>) and assess PRR expression. Symbols, data from individual mice in 2 independent experiments with 4-5 mice per group; means  $\pm$  SEM are also shown (\*,  $P < 0.05$  by Student's t-test).



**Supplemental Figure 6. Expression of PRRs in naïve mice.** PRR profiling of leukocytes from naïve WT (blue circles) or CaMK4 knockout (orange squares) mice. Antibody labeling and flow cytometry were used to classify pulmonary leukocytes as DCs (CD45<sup>+</sup>, CD11b<sup>+</sup>, CD11c<sup>+</sup>, F4/80<sup>-</sup>), exudate or recruited macrophages (CD45<sup>+</sup>, CD11b<sup>+</sup>, CD11c<sup>+</sup>, F4/80<sup>+</sup>), or macrophages/monocytes (CD45<sup>+</sup>, CD11b<sup>+</sup>, CD11c<sup>-</sup>, F4/80<sup>+</sup>) and assess PRR expression. Data from individual mice (5 mice per group) are shown, with means  $\pm$  SEM (\*,  $P < 0.05$  by Student's t-test).

Supplemental Table 1

Gene Symbol	Biological Role	phagocytic index	stdev	adherence index	stdev
ACP1	acid phosphatase 1	1.12	0.24	1.04	0.19
ADCK5	aarF domain containing kinase 5	1.26	0.17	0.89	0.20
AURKB	aurora kinase B	1.05	0.25	0.85	0.27
BCKDK	branched chain ketoacid dehydrogenase kinase	0.98	0.17	1.05	0.14
CAMK4	calcium/calmodulin-dependent protein kinase IV	0.82	0.12	0.89	0.28
CAMKK2	calcium/calmodulin-dependent protein kinase kinase 2, beta	1.08	0.72	1.08	1.00
CDKL5	cyclin-dependent kinase-like 5	0.86	0.21	1.07	0.28
CDKN1A	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	0.69	0.30	1.09	0.31
CDKN3	cyclin-dependent kinase inhibitor 3	1.08	0.09	1.09	0.11
CKMT1B	creatine kinase, mitochondrial 1B	1.13	0.19	1.22	0.23
CNKSR1	connector enhancer of kinase suppressor of Ras 1	1.05	0.35	1.13	0.53
CNKSR3	CNKSR family member 3	1.17	0.22	1.06	0.33
CSNK1A1	casein kinase 1, alpha 1	1.11	0.01	0.86	0.04
CTDSP1	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like	0.91	0.17	1.08	0.25
DGKZ	diacylglycerol kinase, zeta 104kDa	1.17	0.26	0.80	0.25
DLGAP5	discs, large (Drosophila) homolog-associated protein 5	0.82	0.30	0.98	0.40
DUS2L	dihydrouridine synthase 2	0.69	0.14	0.94	0.17
DUSP22	dual specificity phosphatase 22	0.98	0.21	0.88	0.22
EPHA5	EPH receptor A5	2.04	0.22	0.99	0.24
FLT3	fms-related tyrosine kinase 3	1.36	0.26	1.22	0.22
FYN	FYN proto-oncogene, Src family tyrosine kinase	1.30	0.15	1.11	0.09
GNE	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase	0.79	0.09	0.85	0.18
GRK7	G protein-coupled receptor kinase 7	1.71	0.18	1.08	0.17
GUCY2D	guanylate cyclase 2D, membrane (retina-specific)	1.30	0.28	0.98	0.24
IP6K2	inositol hexakisphosphate kinase 2	1.67	0.07	1.40	0.11
IP6K3	inositol hexakisphosphate kinase 3	1.45	0.17	1.06	0.23
KDR	kinase insert domain receptor (a type III receptor tyrosine kinase)	1.69	0.20	0.89	0.15
KSR2	kinase suppressor of ras 2	0.99	0.13	0.93	0.12
LTK	leukocyte receptor tyrosine kinase	0.74	0.17	1.17	0.10
MAP4K2	mitogen-activated protein kinase kinase kinase kinase 2	1.69	0.13	0.67	0.15
MAP4K4	mitogen-activated protein kinase kinase kinase 4	1.24	0.15	1.27	0.25
MAPK13	mitogen-activated protein kinase 13	1.45	0.18	0.61	0.24
MAPK8IP3	mitogen-activated protein kinase 8 interacting protein 3	0.97	0.04	1.18	0.06
MAPKAPK3	mitogen-activated protein kinase-activated protein kinase 3	1.13	0.08	1.20	0.02
MVK	mevalonate kinase	1.13	0.14	1.21	0.18
MYLK	myosin light chain kinase	1.56	0.05	1.11	0.16
NEK2	NIMA (never in mitosis gene a)-related kinase 2	1.05	0.13	0.87	0.13
NLK	nemo-like kinase	0.64	0.16	0.92	0.13
NME7	non-metastatic cells 7, protein expressed in (nucleoside-diphosphate kinase)	1.91	0.24	1.09	0.28
PAK2	p21 protein (Cdc42/Rac)-activated kinase 2	1.08	0.26	1.11	0.32
PAK4	p21 protein (Cdc42/Rac)-activated kinase 4	0.95	0.12	0.94	0.13
PDGFRB	platelet-derived growth factor receptor, beta polypeptide	1.26	0.23	1.00	0.25
PDXK	pyridoxal (pyridoxine, vitamin B6) kinase	1.44	0.18	1.11	0.27
PFKP	phosphofructokinase, platelet	1.05	0.15	1.14	0.27
PHKG2	phosphorylase kinase, gamma 2 (testis)	1.07	0.23	0.83	0.22
PICK1	protein interacting with PRKCA 1	0.76	0.13	1.13	0.26
PIM1	pim-1 oncogene	0.91	0.10	0.81	0.12
PIP4K2C	phosphatidylinositol-5-phosphate 4-kinase, type II, gamma	1.26	0.13	0.98	0.14
PIP5K1L	phosphatidylinositol-4-phosphate 5-kinase-like 1	1.12	0.09	1.02	0.08
PPP1CB	protein phosphatase 1, catalytic subunit, beta isozyme	1.11	0.14	0.94	0.17
PPP1R10	protein phosphatase 1, regulatory subunit 10	1.25	0.03	1.41	0.07
PPP2CB	protein phosphatase 2, catalytic subunit, beta isozyme	0.70	0.16	1.26	0.14
PRKACA	protein kinase, cAMP-dependent, catalytic, alpha	1.24	0.17	0.86	0.13
PRKAR1A	protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)	0.77	0.14	1.07	0.21
PRKCD	protein kinase C, delta	1.33	0.17	1.12	0.26
PRKD1	protein kinase D1	1.63	0.26	1.23	0.19
PRKG1	protein kinase, cGMP-dependent, type I	1.01	0.29	1.05	0.29
PRSS7	protease, serine, 7 (enterokinase)	0.97	0.23	1.16	0.21
PTPN20B	protein tyrosine phosphatase, non-receptor type 20	0.88	0.17	0.61	0.14
PTPN4	protein tyrosine phosphatase, non-receptor type 4	1.29	0.21	0.65	0.20
PTPRH	protein tyrosine phosphatase, receptor type, H	1.07	0.15	0.91	0.19
RNGTT	RNA guanylyltransferase and 5'-phosphatase	1.13	0.05	1.25	0.13
RPS6KA2	ribosomal protein S6 kinase, 90kDa, polypeptide 2	1.19	0.20	0.85	0.21
SBF1	SET binding factor 1	1.04	0.18	1.04	0.27
SCYL3	SCY1-like 3 (S. cerevisiae)	0.72	0.39	1.06	0.48
SH3KBP1	SH3-domain kinase binding protein 1	1.27	0.14	1.11	0.18
SPRYD3	SPRY domain containing 3	1.32	0.22	0.87	0.32
STK36	serine/threonine kinase 36, fused homolog (Drosophila)	1.04	0.18	0.94	0.25
STYXL1	serine/threonine/tyrosine interacting-like 1	1.19	0.29	1.07	0.33
TK1	thymidine kinase 1, soluble	1.27	0.26	1.01	0.33
TPD52L3	tumor protein D52-like 3	1.33	0.37	1.13	0.43
TPK1	thiamin pyrophosphokinase 1	1.14	0.22	0.92	0.25
TRIM24	tripartite motif-containing 24	0.99	0.25	1.10	0.32
TRIM33	tripartite motif-containing 33	1.06	0.17	0.93	0.15
TRRAP	transformation/transcription domain-associated protein	1.17	0.29	1.05	0.34
ULK1	unc-51-like kinase 1 (C. elegans)	0.79	0.12	1.17	0.09
ULK2	unc-51-like kinase 2 (C. elegans)	0.88	0.13	0.73	0.11
ZAP70	zeta-chain (TCR) associated protein kinase 70kDa	0.89	0.31	1.14	0.31
ZMYND8	zinc finger, MYND-type containing 8	1.50	0.26	0.81	0.21

Supplemental Table 2													
Gene Name		<i>C. neo.</i>	<i>C. alb.</i>	<i>S. cer.</i>	<i>E. coli</i>	Latex beads		<i>C. neo.</i>	<i>C. alb.</i>	<i>S. cer.</i>	<i>E. coli</i>	Latex beads	
ADCK5	uptake	1.06	1.16	1.06	1.02	0.97	adherence	1.07	1.28	0.96	1.00	0.97	
	stdev	0.08	0.12	0.11	0.04	0.09	stdev	0.15	0.22	0.06	0.12	0.19	
AURKB	uptake	0.99	0.99	1.03	0.98	1.31	adherence	1.00	1.00	1.04	0.80	1.35	
	stdev	0.20	0.17	0.19	0.32	1.33	stdev	0.24	0.21	0.37	0.40	1.31	
CAMK4	uptake	0.67	0.97	1.02	0.98	0.96	adh	0.95	1.02	1.01	0.92	0.93	
	stdev	0.16	0.13	0.08	0.07	0.04	stdev	0.16	0.17	0.11	0.11	0.15	
CAMKK2	uptake	0.96	1.02	1.03	0.97	1.80	adherence	1.03	1.11	1.07	1.12	1.88	
	stdev	0.12	0.16	0.18	0.33	1.13	stdev	0.17	0.20	0.25	0.51	1.20	
CCL15	uptake	0.91	0.89	0.85	0.85	0.58	adherence	0.93	0.84	0.80	0.78	0.70	
	stdev	0.25	0.16	0.15	0.36	0.12	stdev	0.29	0.17	0.15	0.26	0.16	
CTDSPL	uptake	1.00	1.08	1.05	0.97	0.97	adherence	0.98	1.13	0.97	1.06	1.06	
	stdev	0.12	0.13	0.08	0.08	0.05	stdev	0.17	0.19	0.10	0.15	0.15	
DLGAP5	uptake	1.01	1.03	1.01	0.99	1.00	adherence	0.98	1.09	0.98	0.92	1.06	
	stdev	0.10	0.10	0.05	0.05	0.07	stdev	0.16	0.18	0.11	0.10	0.15	
DUSP22	uptake	0.78	1.05	1.08	0.97	1.00	adherence	1.00	1.12	1.06	0.91	1.08	
	stdev	0.12	0.13	0.08	0.06	0.06	stdev	0.15	0.18	0.12	0.14	0.17	
GNE	uptake	0.65	0.98	1.08	0.97	0.97	adherence	0.98	1.10	1.08	1.02	1.09	
	stdev	0.17	0.14	0.08	0.07	0.04	stdev	0.18	0.27	0.11	0.16	0.13	
LRRK2	uptake	0.93	1.01	0.94	0.89	0.79	adherence	1.09	1.14	0.97	0.82	0.80	
	stdev	0.17	0.17	0.12	0.29	0.16	stdev	0.23	0.20	0.07	0.42	0.22	
MAP4K2	uptake	0.81	0.89	0.84	0.78	0.67	adherence	0.90	0.96	0.92	0.85	0.75	
	stdev	0.21	0.20	0.11	0.33	0.34	stdev	0.18	0.20	0.12	0.38	0.31	
MAPK13	uptake	0.92	0.98	0.92	0.89	1.02	adherence	1.02	1.04	0.96	0.91	1.05	
	stdev	0.13	0.16	0.14	0.39	0.82	stdev	0.15	0.19	0.13	0.56	0.87	
MVK	uptake	0.96	1.04	1.07	0.98	0.98	adherence	1.03	1.14	1.00	1.01	0.95	
	stdev	0.11	0.14	0.09	0.07	0.06	stdev	0.14	0.17	0.11	0.12	0.15	
PHKG2	uptake	1.02	1.08	1.10	1.03	0.98	adherence	1.06	1.11	1.03	1.04	1.01	
	stdev	0.06	0.11	0.10	0.11	0.07	stdev	0.13	0.13	0.11	0.18	0.18	
PIP5K1C	uptake	1.00	1.01	1.01	0.95	0.98	adherence	0.96	1.03	1.02	0.93	0.93	
	stdev	0.09	0.12	0.05	0.08	0.06	stdev	0.12	0.16	0.11	0.13	0.19	
PPP1R10	uptake	0.92	0.94	0.92	0.97	0.75	adherence	0.96	0.94	0.84	0.80	0.76	
	stdev	0.17	0.15	0.12	0.38	0.19	stdev	0.29	0.18	0.12	0.28	0.19	
PRKACA	uptake	0.97	1.02	1.04	0.99	0.95	adherence	0.95	1.03	0.97	0.99	1.00	
	stdev	0.13	0.14	0.07	0.07	0.06	stdev	0.11	0.16	0.12	0.14	0.20	
PRKCD	uptake	1.29	1.44	0.94	1.22	0.70	adherence	1.03	1.12	0.77	0.84	0.81	
	stdev	0.22	0.18	0.12	0.41	0.17	stdev	0.33	0.17	0.16	0.64	0.20	
PRKD1	uptake	1.00	1.00	0.89	0.93	0.64	adherence	1.27	1.00	0.74	0.74	0.70	
	stdev	0.23	0.20	0.09	0.38	0.18	adherence	0.33	0.20	0.13	0.35	0.16	
PTPN20B	uptake	0.92	0.97	0.87	0.83	0.66	adherence	0.84	0.91	0.81	0.81	0.62	
	stdev	0.14	0.19	0.10	0.36	0.25	stdev	0.18	0.15	0.09	0.37	0.20	
RPS6KA2	uptake	0.93	0.99	1.03	0.98	0.96	adherence	0.96	1.02	1.02	1.01	1.05	
	stdev	0.12	0.15	0.08	0.07	0.06	stdev	0.15	0.18	0.14	0.13	0.23	
SCYL3	uptake	0.97	1.07	1.05	1.00	0.96	adherence	0.97	1.17	1.00	1.00	0.98	
	stdev	0.10	0.16	0.09	0.06	0.06	stdev	0.10	0.23	0.07	0.16	0.10	
SPRYD3	uptake	0.99	0.94	0.93	0.91	0.55	adherence	1.07	1.00	0.95	1.07	0.65	
	stdev	0.17	0.25	0.17	0.35	0.14	stdev	0.26	0.17	0.13	0.47	0.18	
TPK1	uptake	0.90	0.90	0.97	0.92	0.92	adherence	0.90	0.91	1.00	0.95	1.06	
	stdev	0.15	0.21	0.10	0.36	0.70	stdev	0.17	0.23	0.08	0.50	0.75	
ULK1	uptake	0.84	0.88	0.83	0.75	0.66	adherence	0.92	0.95	0.83	0.66	0.64	
	stdev	0.24	0.23	0.15	0.29	0.22	stdev	0.29	0.25	0.19	0.46	0.24	



**Supplemental Table 3**

<b>Antigen</b>	<b>Clone</b>	<b>Fluorophore</b>	<b>Company</b>
CD3	17-A2	APC-Cy7	BioLegend
CD4	GK1.5	BUV737	BD Biosciences
CD8a	53-6.7	BV650	BD Biosciences
CD11b	M1/70	BV510	BD Biosciences
CD11c		PE	Affymetrix
CD19	1D3	BV786	BD Biosciences
CD45	30-F11	Pacific Blue	BioLegend
F4/80	BM8	APC	Thermo
F4/80	BM8	PE-Cy7	Affymetrix
Ly-6G	1A8	BV711	BD Biosciences
Siglec-F	E50-2440	PE-CF594	BD Biosciences
CD14	rmC5-3	Alexa Fluor 647	BD Biosciences
CD16/CD32	2.4G2	APC	BD Biosciences
CD18	C71/16	APC	BD Biosciences
CD21/CD35	7G6	APC	BD Biosciences
CD36	CRF D-2712	APC	BD Biosciences
CD206	MR5D3	Alexa Fluor 647	BD Biosciences
CD282	6C2	Alexa Fluor 647	BD Biosciences
Clec6A/Dectin-2	Polyclonal	APC	R&D
Clec7A/Dectin-1	218820	APC	R&D
DNGR1	10B4	Alexa Fluor 647	BD Biosciences