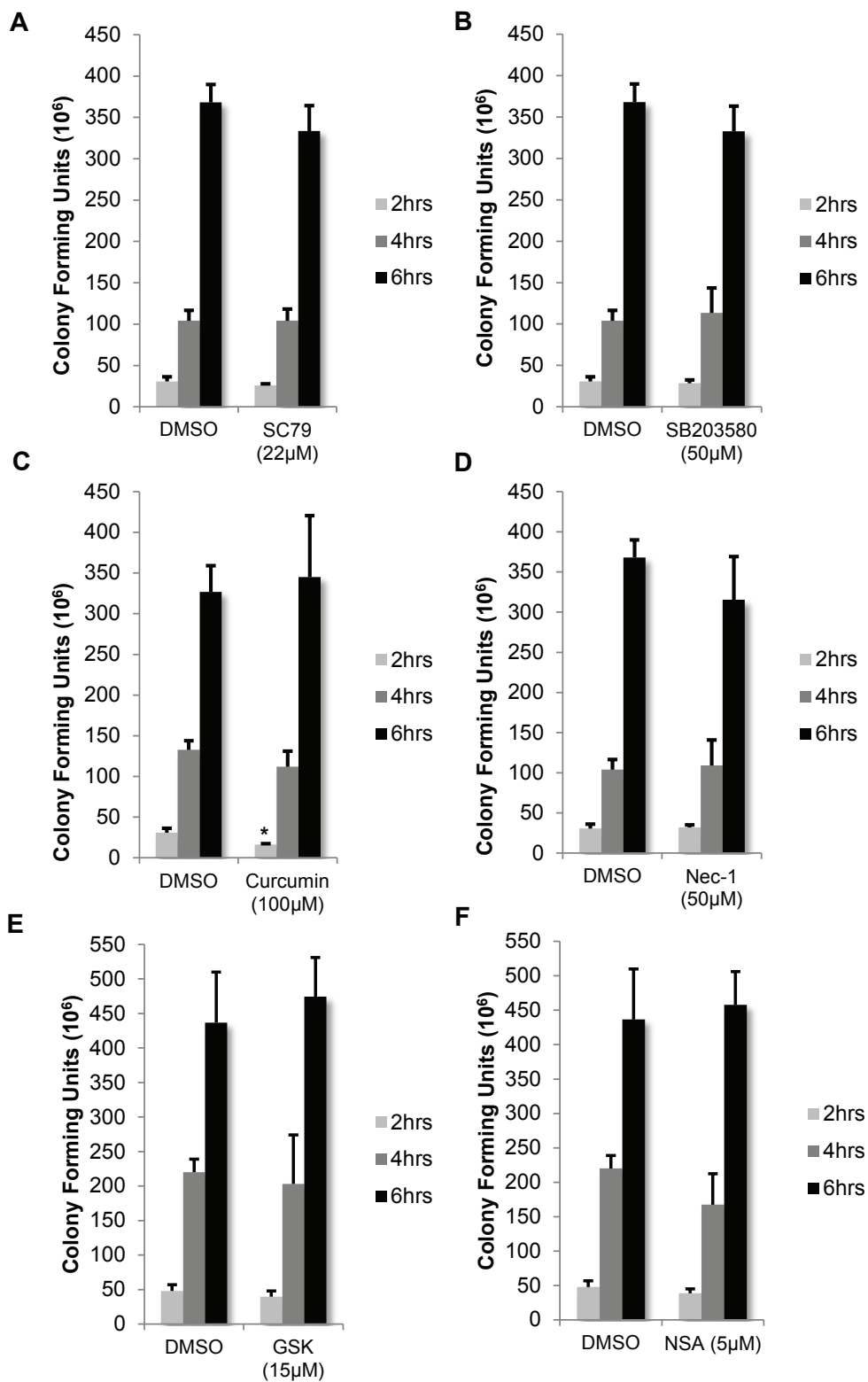
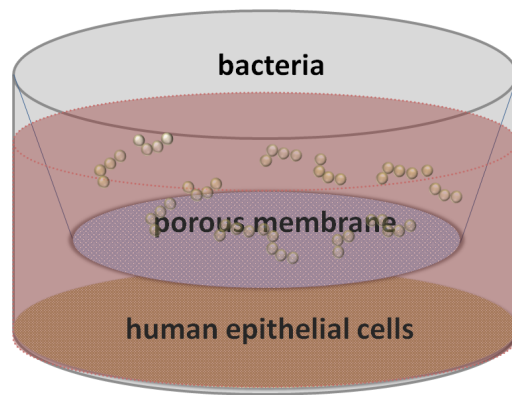


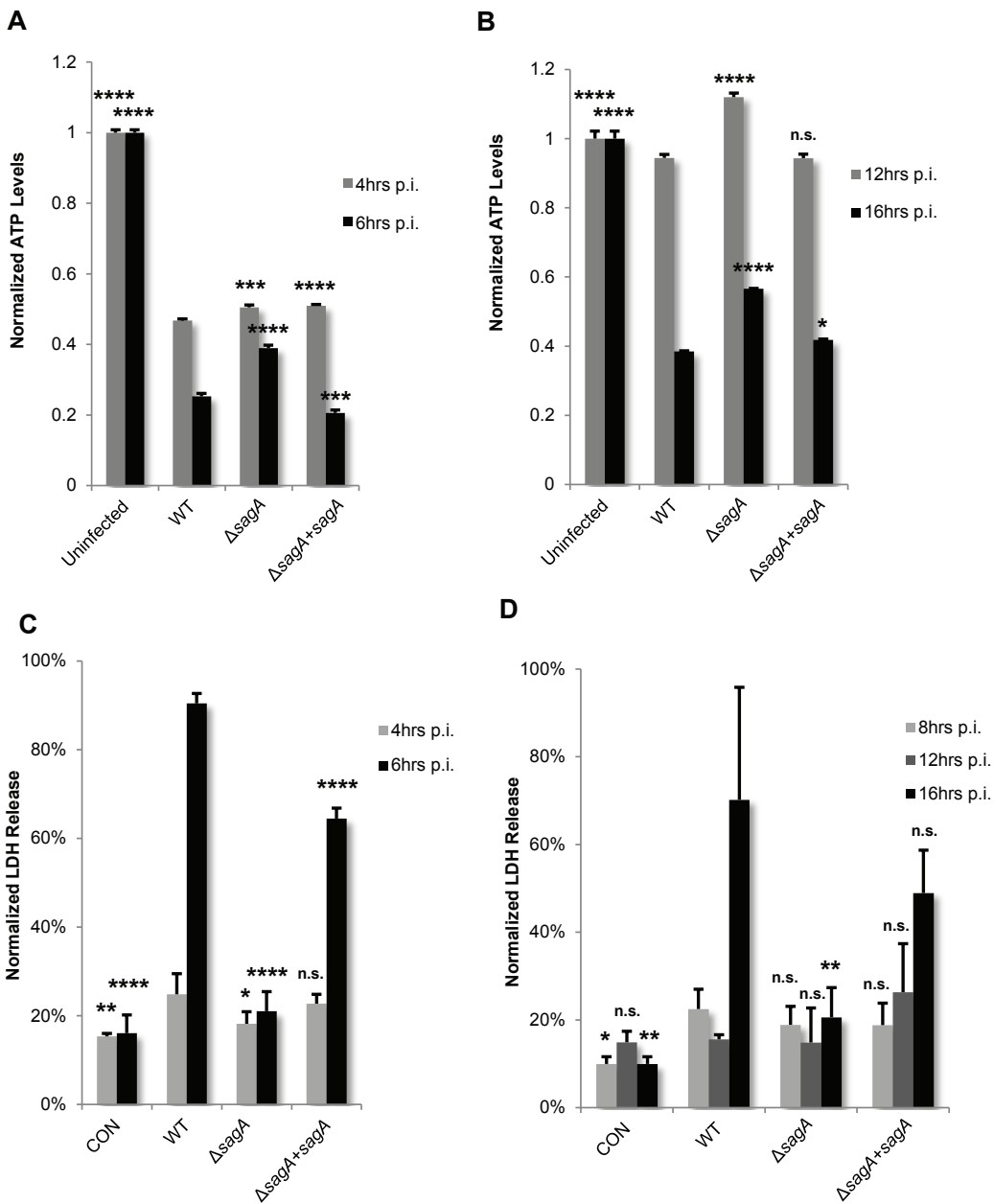
Supplementary Figure 1: (A) The Streptolysin S associated gene (*sag*) cluster encodes the protoxin portion of Streptolysin S, several enzymes that play critical roles in processing SLS to produce the mature toxin, and additional protein products believed to be involved in toxin transport (adapted from Lee et al. 2008). (B) Presence of an intact *sag* cluster induces robust lysis when WT GAS is grown on sheep blood agar. This lytic phenotype is lost when SLS-deficient GAS, lacking *sagA*, are grown on blood plates and restored with complementation of the WT *sagA* gene in the  $\Delta sagA$  background.



Supplementary Figure 2: Effects of inhibitor and activator compounds on bacterial growth and viability. Bacteria were grown in DMEM+10% FBS supplemented with the highest compound concentration that had provided significantly increased protection from GAS-induced cell death in the ethidium homodimer assay. (A-F) At 2, 4, and 6hrs, bacteria were plated on Todd-Hewitt agar and their growth in the presence of each compound, compared to DMSO, was determined by a colony counting assay. Significance between each vehicle control (DMSO) and each treatment at the corresponding time point was determined by an unpaired, two-tailed Student's t-test.

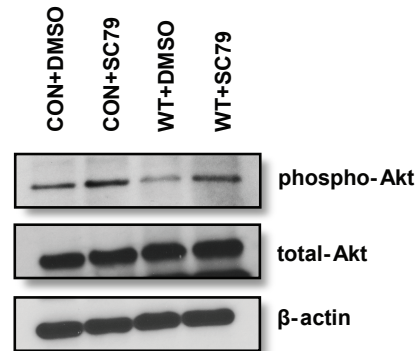


Supplementary Figure 3: Diagram of Transwell system for assessing the effects of secreted bacterial factors on host cells. Human keratinocytes are plated in the bottom compartment and grown to 90% confluence. A collagen coated membrane with 0.4 $\mu$ m pores separates the upper and lower chambers, and bacteria are added to the upper chamber of the Transwell system.

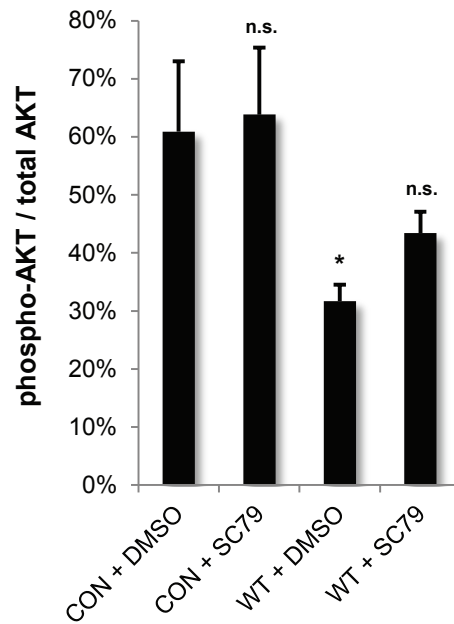


Supplementary Figure 4: ATP loss and LDH release confirm SLS-dependent loss of keratinocyte viability during Group A *Streptococcal* infection. HaCaT cells were infected with GAS for 4-6 hours using the direct infection system (A and C) or for 8-16hrs using the Transwell infection system (B and D). ATP determination assays (A and B) and LDH release assays (C and D) were used to compare keratinocyte viability in response to infection. (A and B) Technical replicates (n=3) from one representative biological replicate ( $2 \times 10^6$  cells per sample) were averaged for each condition, with error bars representing standard deviation. (C and D) Averages from three independent biological replicates are shown, with error bars representing standard deviation. Overall p-values were determined by ANOVA (A) 4hrs,  $p < 0.0001$ ; 6hrs,  $p < 0.0001$  (B) 12hrs,  $p < 0.0001$ ; 16hrs,  $p < 0.0001$  (C) 4hrs,  $p = 0.0059$ ; 6hrs,  $p < 0.0001$  (D) 8hrs,  $p = 0.0287$ ; 12hrs,  $p = 0.1977$ ; 16hrs,  $p = 0.0031$ . Dunnett's tests were performed to compare each condition with wild-type infection for the corresponding time point and infection system.

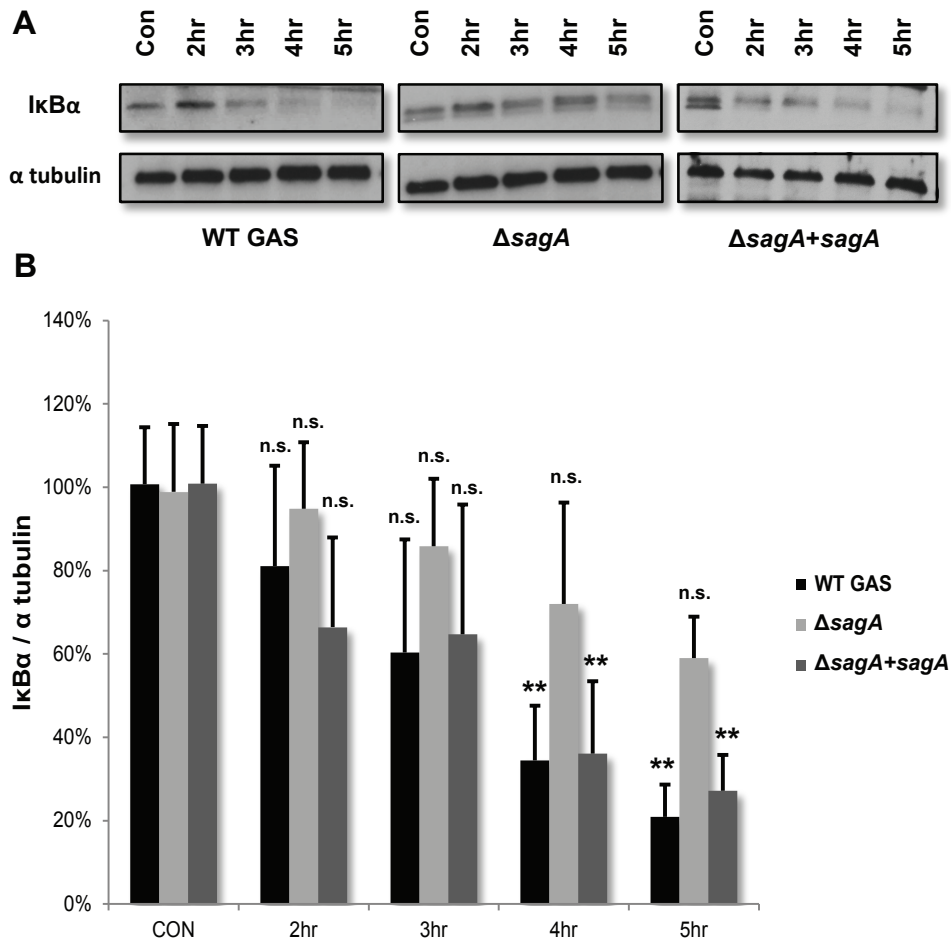
**A**



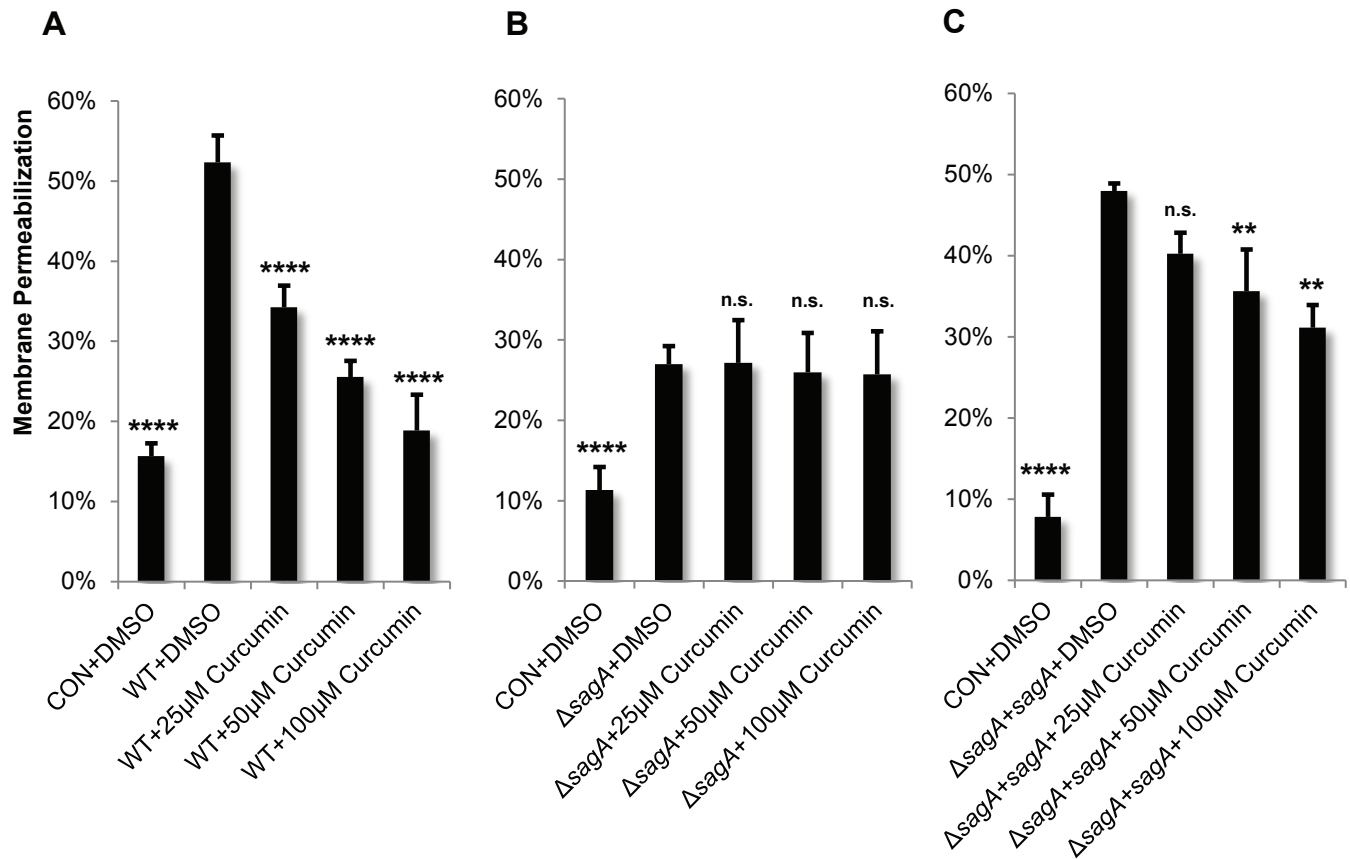
**B**



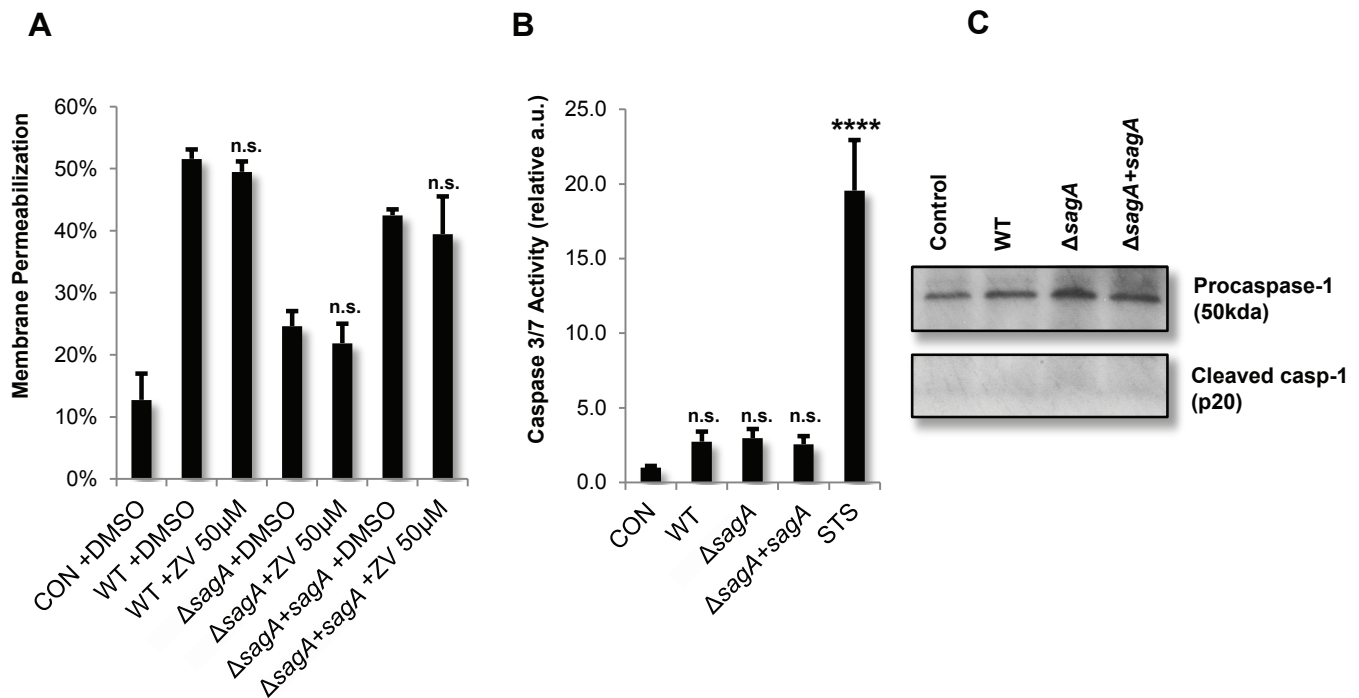
Supplementary Figure 5: SC79 enhances Akt phosphorylation in HaCaT cells during GAS infection. (A) HaCaT keratinocytes were pretreated with SC79 (22 $\mu$ M) or DMSO for 1.5hrs and infected with GAS directly for 4hrs at an MOI of 10. (B) Densitometry from three independent Western Blots showing phospho-Akt/total Akt levels for uninfected or GAS-infected cells. Error bars represent standard deviation from the mean. Significance was determined by ANOVA ( $p=0.0058$ ) followed by Dunnett's test to compare all conditions to the uninfected vehicle control condition (CON+DMSO).



Supplementary Figure 6: Streptolysin S contributes to I $\kappa$ B loss during Group A *Streptococcal* infection. HaCaT keratinocytes were infected with GAS for 2-5hrs at MOI=10 and lysates were assessed for changes in total I $\kappa$ B levels by Western Blotting (A). Densitometry from three independent Western Blots was performed to quantify the relative abundance of I $\kappa$ B, compared to  $\alpha$ -tubulin, over the course of GAS infection (B). Averages from three biological replicates are shown, with error bars representing standard deviation. The overall p-value for each strain was determined by ANOVA (WT, p=0.002;  $\Delta$ sagA, p=0.0853;  $\Delta$ sagA+sagA, p=0.0083), and Dunnett's tests were performed to compare each infection condition for each strain with the corresponding uninfected control condition.

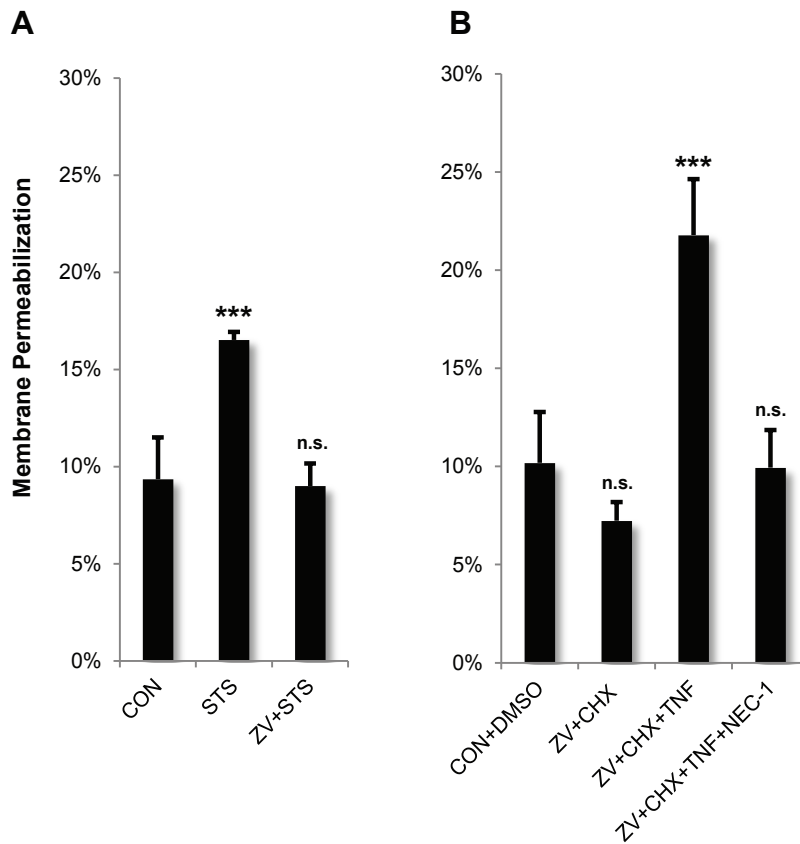


Supplementary Figure 7: Inhibition of the NFκB inflammatory signaling cascade significantly reduces GAS-induced cell death. HaCaTs were treated for 1.5hrs with the NFκB inhibitor curcumin prior to infection with WT or mutant GAS for 6hrs at an MOI of 10. Cell death was determined by ethidium homodimer membrane permeabilization assay. Each condition was tested in triplicate and error bars represent standard deviation from the mean. Use of the inhibitor during bacterial infection significantly reduced cell death compared to vehicle control treatments in GAS-infected cells. The overall p-value for each strain was determined by ANOVA (A)  $p < 0.0001$  (B)  $p < 0.0001$  (C)  $p < 0.0001$ . Dunnett's tests were performed post hoc to compare each condition to the corresponding vehicle control infection (i.e. WT+DMSO).

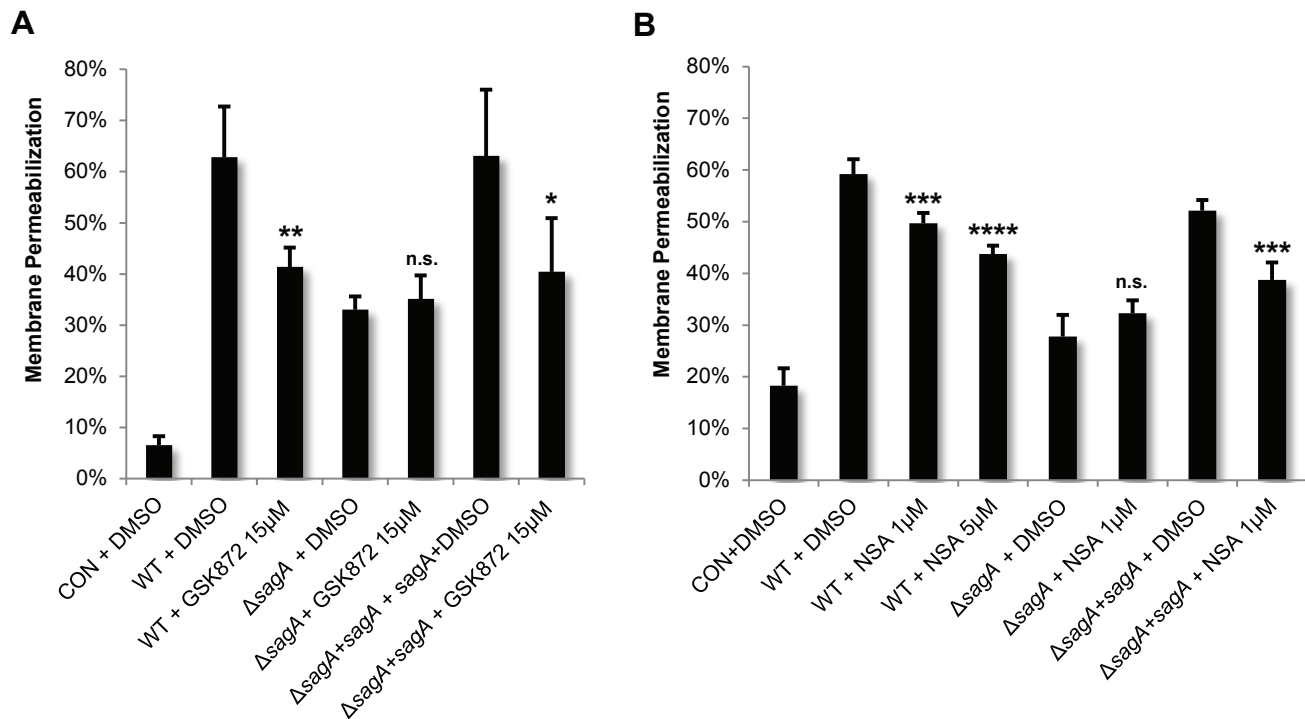


Supplementary Figure 8: Caspase activation is not required for SLS-mediated keratinocyte death during GAS infection. (A) HaCaTs were treated for 1hr with the pan-caspase inhibitor Z-VAD-fmk (50 $\mu$ M) prior to infection with GAS for 6hrs at an MOI of 10. Inhibitor treatment during bacterial infection did not significantly reduce cell death compared to vehicle control treatments in WT or SLS-mutant GAS. Significance was determined by ANOVA ( $p < 0.0001$ ) followed by Dunnett's test ( $p < 0.05$  was considered significant). (B) Caspase 3/7 activation was assessed by infecting keratinocytes directly with WT, SLS-deficient, or  $\Delta$ sagA+sagA GAS for 6hrs at an MOI of 10. Staurosporine (2 $\mu$ M) was used as a positive control. Caspase 3/7 activity levels were measured using the luminescence-based CaspaseGLO kit from Promega and normalized relative to uninfected control cells. None of the GAS infection conditions significantly induced caspase 3/7 activity compared to uninfected controls at 6hrs post-infection. In contrast, staurosporine induced robust activation of caspases compared to uninfected cells. Significance was determined by ANOVA ( $p < 0.0001$ ) and a post hoc Dunnett's test. (C) Activity of caspase-1 was evaluated by Western Blotting following infection for 5hrs at an MOI of 10. Levels of cleaved caspase 1 were not found to be increased in the presence of GAS compared to uninfected cells.





Supplementary Figure 9: Effects of known apoptosis-inducing and programmed necrosis-inducing compounds on HaCaT keratinocyte membrane permeabilization and death by ethidium homodimer assay. (A) Staurosporine (STS) at a concentration of 2 $\mu$ M was incubated with HaCaT cells for 6hrs prior to determining membrane permeabilization; use of the general caspase inhibitor Z-vad-fmk (ZV) at 50 $\mu$ M 1.5hrs prior to the addition of STS was able to completely inhibit the membrane permeabilization induced by STS as well as reducing other signs of cellular distress such as rounding and detachment. Significance was determined by ANOVA ( $p < 0.0001$ ) followed by Dunnett's test to compare values to uninfected cells. (B) The combined treatment of Z-vad-fmk (10 $\mu$ M; added 1.5hrs prior to CHX and TNF $\alpha$ ), cycloheximide (CHX; 50 $\mu$ M) and TNF $\alpha$  (100ng/mL) induced membrane permeabilization and death in HaCaT keratinocytes 6hrs post-treatment. Use of the programmed necrosis inhibitor Necrostatin-1 (Nec-1; 50 $\mu$ M) administered along with ZV 1.5hrs prior to the addition of CHX and TNF $\alpha$  was able to reduce cell death to control levels. Significance was determined using ANOVA ( $p < 0.0001$ ) followed by Dunnett's test to compare values to uninfected cells.



Supplementary Figure 10: RIPK3 and MLKL contribute to the activation of programmed cell death in GAS-infected keratinocytes. HaCaTs were incubated with the RIPK3 kinase inhibitor GSK872 (A) or the MLKL inhibitor NSA (B) for 1.5hrs prior to infection with GAS at MOI=10. Cell death was determined by ethidium homodimer membrane permeabilization assay 6hrs post-infection. The averages of three biological replicates are shown for each condition, and error bars represent standard deviation. Overall p-values were determined by ANOVA; (A)  $p < 0.0001$  (B)  $p < 0.0001$ . Dunnett's tests were performed post hoc to compare vehicle control means from each strain (i.e. WT+DMSO) to uninfected control cells (CON+DMSO) and the corresponding pharmacological treatment (i.e. WT+GSK872). P-values for each vehicle control matched to each GAS strain versus treatment with the inhibitors are indicated.





ID	Company	Year	Revenue	Profit	Assets	Liabilities	Equity	Debt	Interest	Dividend	EPS	Market Cap	Share Price	Volume	Turnover	ROE	ROA	ROIC	Operating Margin	Net Margin	Capital Expenditure	Research & Development	SG&A	Goodwill	Intangible	Restructuring	Other	Notes
001	Apple	2022	394.31	106.33	339.48	220.01	119.47	120.00	0.00	0.00	0.99	299.00	173.98	17.39	1.39	15.8%	10.8%	12.5%	20.3%	16.8%	1.12	1.12	0.00	0.00	0.00	0.00	NP 0010482.2	278.256
002	Microsoft	2022	311.50	85.21	308.70	191.14	117.53	121.17	0.00	0.00	1.15	328.00	143.07	37.27	1.34	21.3%	13.0%	17.4%	23.7%	19.8%	0.87	0.87	0.00	0.00	0.00	0.00	NP 0010989	595.710
003	Amazon	2022	376.36	24.26	341.10	258.45	82.65	158.45	0.00	0.00	0.55	330.00	133.07	29.29	1.30	13.7%	9.7%	11.6%	11.3%	10.3%	1.10	1.10	0.00	0.00	0.00	0.00	NP 0010958.1	649.419
004	Google	2022	281.75	89.66	292.99	199.94	103.05	189.94	0.00	0.00	1.00	310.00	155.12	26.45	1.30	18.5%	11.3%	15.8%	20.5%	17.5%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	608.637
005	Facebook	2022	252.32	29.97	282.29	212.32	69.97	112.32	0.00	0.00	0.48	290.00	116.12	18.18	1.29	11.9%	7.9%	10.3%	12.8%	11.2%	1.08	1.08	0.00	0.00	0.00	0.00	NP 0010946.7	418.141
006	Netflix	2022	31.60	5.43	37.03	21.17	15.86	21.17	0.00	0.00	0.60	35.00	13.44	3.84	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010796.5	314.119
007	Alphabet	2022	281.75	89.66	292.99	199.94	103.05	189.94	0.00	0.00	1.00	310.00	155.12	26.45	1.30	18.5%	11.3%	15.8%	20.5%	17.5%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010482.2	549.419
008	Tesla	2022	56.48	5.54	62.02	46.48	15.54	15.54	0.00	0.00	0.39	60.00	23.24	6.36	1.28	20.8%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
009	Uber	2022	23.01	0.00	23.01	16.10	6.91	16.10	0.00	0.00	0.00	23.00	10.00	2.30	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010796.5	314.119
010	Twitter	2022	1.11	0.00	1.11	0.00	1.11	1.11	0.00	0.00	0.00	1.10	0.00	0.11	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
011	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
012	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
013	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
014	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
015	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
016	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
017	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
018	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
019	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141
020	Zoom	2022	4.01	0.00	4.01	0.00	4.01	4.01	0.00	0.00	0.00	4.00	0.01	0.01	1.28	19.1%	11.2%	15.8%	18.1%	16.8%	0.82	0.82	0.00	0.00	0.00	0.00	NP 0010484.2	418.141













VEGET (KOR)	Parasitic	0.0	451	1193	4772	0.0	495	0.96	4345	-36	-0.55	-151	-48	-172	16	3	NP 002585	20710
VEGET (KOR)	Parasitic	0.0	488	420	1214	0.0	274	4.43	1101	-48	0.57	0.13	-54	-207	16	3	NP 002584	23565
VEGET (KOR)	Parasitic	0.0	183	1037	1037	0.0	826	6.14	931	-55	-0.92	-0.29	-57	-57	16	4	NP 002584	23565
VEGET (KOR)	Parasitic	0.0	3394	3338	1189	0.0	1266	7.92	1023	45	-0.79	-0.29	-33	-33	16	7	NP 004083	24342
VEGET (KOR)	Parasitic	0.0	2037	1544	1106	0.0	1934	0.17	1035	-48	-0.52	-0.39	-45	-45	16	6	NP 003381	23201
VEGET (KOR)	Parasitic	0.0	2544	437	1138	0.0	1853	10.84	1084	-38	-0.29	-0.12	-18	-18	16	5	NP 001070	24342
VEGET (KOR)	Parasitic	0.0	7952	1708	1331	0.0	6944	5.42	1246	24	1.14	0.91	-20	-20	16	5	NP 004544	23747
VEGET (KOR)	Parasitic	0.0	2066	0.79	1145	0.0	1925	8.37	1035	42	0.48	-0.48	-22	-22	16	6	NP 003168	24342
VEGET (KOR)	Parasitic	0.0	3187	1703	1171	0.1	2429	11.17	1117	24	0.45	0.22	-0.24	-0.24	16	8	NP 003168	24342
VEGET (KOR)	Parasitic	0.0	1591	437	1235	0.0	88	12.13	434	-38	-1.73	-2.27	48	-207	16	8	NP 001070	24342
VEGET (KOR)	Parasitic	0.0	1672	430	1072	0.0	1556	3.81	1011	-50	-0.32	-0.35	-12	-12	16	6	NP 001338	24342
VEGET (KOR)	Parasitic	0.0	974	811	1005	0.0	707	0.52	339	12	0.87	-0.74	-10	-10	16	7	NP 001338	24342
VEGET (KOR)	Parasitic	0.0	5651	941	1244	0.0	4864	3.34	1220	-12	0.41	-0.33	-15	-15	16	10	NP 001338	24342
VEGET (KOR)	Parasitic	0.0	1243	120	1302	0.0	850	13.19	1319	-21	1.45	1.30	-16	-16	16	10	NP 001338	24342
VEGET (KOR)	Parasitic	0.0	4577	1487	1223	0.0	2816	2.95	1144	-36	0.72	0.96	-138	-138	16	10	NP 001338	24342

**Supplementary Table 2: Significant Changes in Total and Activated Protein Levels in WT vs. *ΔsagA* Infection**

Target Protein Name	Phospho Site (Human)	Full Target Protein Name	Fold Change	Z-ratio WT vs <i>ΔsagA</i>
Hsp27	S82	Heat shock 27 kDa protein beta 1 (HspB1)	8.36	3.71
IκBa	Pan-specific	Inhibitor of NF-kappa-B alpha (MAD3)	6.97	3.55
FAK	Y576	Focal adhesion protein-tyrosine kinase	5.48	3.01
Mnk1	T250+T255	MAP kinase-interacting protein-serine kinase 1 (calmodulin-activated)	5.09	3.34
RSK1/2	S380/S386	Ribosomal S6 protein-serine kinase 1/2	4.79	2.59
Smad1/5/8	S463+S465/S463+S465/S465+S467	Mothers against decapentaplegic homologs 1/5/8	3.78	2.40
Csk	Pan-specific	C-terminus of Src tyrosine kinase	3.55	2.73
STAT5A	Y694	Signal transducer and activator of transcription 5A	3.20	2.08
STAT1a	Y701	Signal transducer and activator of transcription 1 alpha	3.10	1.74
S6Kb1	T412	Ribosomal protein serine S6 kinase beta 1	2.93	2.07
Synapsin 1	S9	Synapsin 1 isoform Ia	2.92	1.85
STAT3	Y705	Signal transducer and activator of transcription 3	2.87	1.92
COX2	Pan-specific	Cyclo-oxygenase 2 (prostaglandin G/H synthase 2 precursor)	2.85	2.25
SNCA	S129	Alpha-synuclein	2.82	2.10
CPG16/CaMKKinase VI	Pan-specific	Serine/threonine-protein kinase DCAMKL1	2.81	2.27
RSK1/2/3	T573/T577/T570	Ribosomal S6 protein-serine kinase 1/2/3	2.80	2.01
STAT3	S727	Signal transducer and activator of transcription 3	2.58	2.03
MST1	Pan-specific	Mammalian STE20-like protein-serine kinase 1 (KRS2)	2.57	2.22
Huntingtin	S421	Huntington's disease protein	2.56	2.19
Shc1	Y349	SH2 domain-containing transforming protein 1	2.54	2.12
Hsp90a/b	Pan-specific	Heat shock 90 kDa protein alpha/beta	2.50	2.01
RSK1/3	T359+S363/T356+S360	Ribosomal S6 protein-serine kinase 1/3	2.49	1.76
Crystallin aB	Pan-specific	Crystallin alpha B (heat-shock 20 kDa like-protein)	2.48	2.31
Rb	Pan-specific	Retinoblastoma-associated protein 1	2.43	2.13
Bcr	Y177	Breakpoint cluster region protein	2.42	2.03
p27 Kip1	T187	p27 cyclin-dependent kinase inhibitor 1B	2.40	1.04
JNK1 (MAPK8)	Pan-specific	Jun N-terminus protein-serine kinase (stress-activated protein kinase (SAPK)) 1	2.31	2.05
S6Kb1	Pan-specific	Ribosomal protein-serine S6 kinase beta 1	2.24	1.22
Smad2	T200	Mothers against decapentaplegic homolog 2	2.21	1.97
SOCS4	Pan-specific	Suppressor of cytokine signalling 4 (SOCS7)	2.21	2.06
FKHRL1	T32	Forkhead-like transcription factor 1 (FOXO3A)	2.19	1.76
Cofilin 1	Pan-specific	Cofilin 1	2.17	1.84
SNCA	Y136	Alpha-synuclein	2.12	1.72
Smad2/3	Pan-specific	SMA- and mothers against decapentaplegic homolog 2/3	2.10	1.82
Smad2	S467	Mothers against decapentaplegic homolog 2	2.01	1.92
S6K	S411	p70 ribosomal protein-serine S6 kinase	1.99	1.89
S6K	S424	p70 ribosomal protein-serine S6 kinase	1.98	1.88
STAT3	Pan-specific	Signal transducer and activator of transcription 3 (acute phase response factor)	1.93	1.15
STAT3	Y705	Signal transducer and activator of transcription 3	1.91	1.93
GSK3a	Pan-specific	Glycogen synthase-serine kinase 3 alpha	1.87	1.73
Crystallin aB	Pan-specific	Crystallin alpha B (heat-shock 20 kDa like-protein)	1.84	1.77
JNK1/2/3	Pan-specific	Jun N-terminus protein-serine kinase (stress-activated protein kinase (SAPK)) 1/2/3	1.76	1.40
S6Kb1	T444+S447	Ribosomal protein serine S6 kinase beta 1	1.71	1.59
Src	Y530	Src proto-oncogene-encoded protein-tyrosine kinase	1.71	1.70
IRS1	S312	Insulin receptor substrate 1	1.67	1.49
GroEL	Pan-specific	GroEL homolog (may correspond to Hsp60)	1.66	1.71
MEKK2 (MAP3K2)	Pan-specific	MAPK/ERK kinase kinase 2	1.66	1.71
STAT2	Y690	Signal transducer and activator of transcription 2	1.65	1.40
SOD (Mn)	Pan-specific	Superoxide dismutase [Mn]	1.65	1.48
Cofilin 1	S3	Cofilin 1	1.64	1.56
Smac/DIABLO	Pan-specific	Second mitochondria-derived activator of caspase	1.64	1.61
PKCa/b2	T638/T641	Protein-serine kinase C alpha/beta 2	1.63	1.05
SOX9	S181	SRY (sex determining region Y)-box 9 (campomelic dysplasia, autosomal sex-reversal)	1.62	1.86
GluR1	S849	Glutamate receptor 1	1.60	1.70
STAT5A	S780	Signal transducer and activator of transcription 5A	1.60	1.44
Acetylated Lysine	Pan-specific	Acetylated Lysine	1.60	1.52
IKKa	S180	Inhibitor of NF-kappa-B protein-serine kinase alpha (CHUK)	1.58	0.99
MKP2	Pan-specific	MAP kinase phosphatase 2 (VH2)	1.58	1.51
Msk1	S376	Mitogen & stress-activated protein-serine kinase 1	1.58	1.32
Src	Pan-specific	Src proto-oncogene-encoded protein-tyrosine kinase	1.56	1.30
MEK2 (MAP2K2)	Pan-specific	MAPK/ERK protein-serine kinase 2 (MKK2)	1.51	1.18
S6Kb2	Pan-specific	Ribosomal protein-serine S6 kinase beta 2	1.50	1.45
CaMK1d	Pan-specific	Calcium/calmodulin-dependent protein-serine kinase 1 delta	1.47	1.54
RSK2	Pan-specific	Ribosomal S6 protein-serine kinase 2	1.46	1.18
MEK4 (MAP2K4)	Pan-specific	MAPK/ERK protein-serine kinase 4 (MKK4)	1.46	1.20
Fyn	Pan-specific	Fyn proto-oncogene-encoded protein-tyrosine kinase	1.44	1.54
SMC1	S957	Structural maintenance of chromosomes protein 1A	1.42	1.38
MEK4 (MAP2K4)	Pan-specific	MAPK/ERK protein-serine kinase 4 (MKK4)	1.40	1.40
MST1	Pan-specific	Mammalian STE20-like protein-serine kinase 1 (KRS2)	1.37	1.07

IRAK2	Pan-specific	Interleukin 1 receptor-associated kinase 2	1.36	1.26
MEK6 (MAP2K6)	Pan-specific	MAPK/ERK protein-serine kinase 6 (MKK6)	1.36	1.31
Src	Pan-specific	Src proto-oncogene-encoded protein-tyrosine kinase	1.36	1.24
SODD	Pan-specific	Silencer of death domains (Bcl2 associated athanogene 4 (BAG4))	1.32	1.36
MEK1/2 (MAP2K1/2)	Pan-specific	MAPK/ERK protein-serine kinase 1/2 (MKK1/2)	1.32	0.97
CASP7	Pan-specific	Caspase 7 (ICE-like apoptotic protease 3 (ICE-LAP3), Mch3)	1.28	1.23
PTEN	S380+T382+T383	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and protein phosphatase and tensin homolog deleted on chromosome 10	1.28	1.28
Src	Pan-specific	Src proto-oncogene-encoded protein-tyrosine kinase	1.28	1.33
STAT1a	Pan-specific	Signal transducer and activator of transcription 1 alpha	1.25	1.45
Hsp40	Pan-specific	DnaJ homolog, subfamily B member 1	1.25	1.09
MEKK4 (MAP3K4)	Pan-specific	MAPK/ERK kinase kinase 4	1.24	1.12
STAT5A	Y694	Signal transducer and activator of transcription 5A	1.23	1.17
SPHK1	Pan-specific	Sphingosine kinase 1	1.21	1.13
JNK1/2/3	Pan-specific	Jun N-terminus protein-serine kinase (stress-activated protein kinase (SAPK)) 1/2/3	1.21	0.99
PSD-95	Pan-specific	Disks large homolog 4	1.20	1.25
ILK1	Pan-specific	Integrin-linked protein-serine kinase 1	1.19	1.22
Gab1	Y627	GRB2-associated binder 1	1.17	1.16
PTEN	S380+T382+T383	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and protein phosphatase and tensin homolog deleted on chromosome 10	1.17	1.18
RSK1	Pan-specific	Ribosomal S6 protein-serine kinase 1	1.16	1.15
GNB2L1	Pan-specific	Guanine nucleotide-binding protein beta (receptor for activated C kinase 1 (RACK1))	1.15	1.12
RelB	Pan-specific	Transcription factor RelB	1.15	1.31
S6Kb1	Pan-specific	Ribosomal protein-serine S6 kinase beta 1	1.14	1.00
Striatin	Pan-specific	Striatin	1.14	1.37
AK2	Pan-specific	Adenylate kinase 2	1.14	1.00
RSK1	S363	Ribosomal S6 protein-serine kinase 1	1.14	1.17
Connexin 43	S368	Gap junction alpha-1 protein	1.12	1.21
MSH2	Pan-specific	DNA mismatch repair protein mutS homolog2, colon cancer, nonpolyposis type 1	1.12	1.13
Synapsin 1	Pan-specific	Synapsin 1 isoform la	1.11	1.12
FRS2	Y348	Fibroblast growth factor receptor substrate 2	1.10	1.31
SOD (Cu/Zn)	Pan-specific	Superoxide dismutase 1	1.08	1.12
Myc	T58	Myc proto-oncogene protein	1.08	1.20
MEKK1 (MAP3K1)	Pan-specific	MAPK/ERK kinase kinase 1	1.08	0.95
RSK1	T348	Ribosomal S6 protein-serine kinase 1	1.08	1.22
TAO3 (JIK)	Pan-specific	STE20-like protein-serine kinase	1.06	0.99
Bcl-xS/L	Pan-specific	Bcl2-like protein 1	1.04	1.14
BRD2	Pan-specific	Bromodomain-containing protein-serine kinase 2	1.01	0.95
SPHK2	Pan-specific	Sphingosine kinase 2	1.00	0.96
JAK1	Y1034	Janus protein-tyrosine kinase 1	0.98	0.95
MEK2 (MAP2K2)	T394	MAPK/ERK protein-serine kinase 2 (MKK2)	0.97	1.03
GSK3a	Y279	Glycogen synthase-serine kinase 3 alpha	0.97	1.05
Hsp90a/b	Pan-specific	Heat shock 90 kDa protein alpha/beta	0.96	1.01
BRCA1	S1423	Breast cancer type 1 susceptibility protein	0.92	0.99
RSK1/2	S380/S386	Ribosomal S6 protein-serine kinase 1/2	0.92	1.07
PRK2 (PKN2)	Pan-specific	Protein kinase C-related protein-serine kinase 2	0.90	1.04
Shc1	Y349+Y350	SH2 domain-containing transforming protein 1	0.89	1.21
Tau	S516	Microtubule-associated protein tau	0.84	0.95
GRK2 (BARK1)	Pan-specific	G protein-coupled receptor-serine kinase 2	0.84	1.09
MEK3 (MAP2K3)	Pan-specific	MAPK/ERK protein-serine kinase 3 (MKK3)	0.82	0.96
ROK $\alpha$ (ROCK2)	Pan-specific	RhoA protein-serine kinase alpha	0.81	0.97
MLC(MLRC2)	S19	Myosin regulatory light chain 2, smooth muscle isoform	0.79	1.11
Cofilin 2	S3	Cofilin 2	0.79	0.99
GRK2 (BARK1)	S670	G protein-coupled receptor-serine kinase 2	0.69	0.97
IRS1	Y1179	Insulin receptor substrate 1	0.63	0.96
PARP1	Pan-specific	Poly [ADP-ribose] polymerase 1 (ADPRT)	-0.27	-1.09
AMPK $\alpha$ 1/2	T183	5'-AMP-activated protein kinase subunit alpha 1/2	-0.31	-1.00
p53	S392	Tumor suppressor protein p53 (antigenNY-CO-13)	-0.34	-1.16
IGF1Rb/IRb	Y1161/Y1185	Insulin-like growth factor 1 /Insulin receptorreceptor beta	-0.36	-1.05
p38 $\alpha$ MAPK	T180+Y182	Mitogen-activated protein-serine kinase p38 alpha	-0.39	-1.14
Plk2	Pan-specific	Polo-like protein kinase 2 (serum -inducible kinase (SNK))	-0.39	-0.96
Jun	Pan-specific	Jun proto-oncogene-encoded AP1 transcription factor	-0.41	-0.97
CASP3	Pan-specific	Caspase 3 (apopain, cysteine protease CPP32)	-0.41	-1.07
EFNB2	Y316	EPH-related receptor tyrosine kinase ligand 5	-0.41	-1.08
PKM2	Pan-specific	Pyruvate kinase, isozymes M1/M2	-0.42	-1.03
EFNA5	Pan-specific	Ephrin-A5	-0.42	-0.98
eIF2a	Pan-specific	Eukaryotic translation initiation factor 2 alpha	-0.43	-1.01
CASP1	Pan-specific	Caspase 1 (Interleukin-1 beta convertase)	-0.45	-1.23
CDKL1	Pan-specific	Cyclin-dependent kinase-like 1	-0.45	-1.30
Tyro10 (DDR2)	Pan-specific	Neurotrophic receptor-tyrosine kinase of discoidin domain receptor family, member 2 precursor	-0.46	-0.99
Elk-1	Pan-specific	ETS domain-containing protein Elk-1	-0.46	-1.05
DNAPK	Pan-specific	DNA-activated protein-serine kinase	-0.48	-1.01
PDK1	Pan-specific	3-phosphoinositide-dependent protein-serine kinase 1	-0.48	-1.42

<b>PKR1</b>		Pan-specific	Double-stranded RNA-dependent protein-serine kinase (EIF2AK2)	-0.49	-1.05
<b>PKBa (Akt1)</b>		T308	Protein-serine kinase B alpha	-0.49	-1.68
<b>EGFR</b>		Y1197	Epidermal growth factor receptor-tyrosine kinase	-0.50	-1.10
<b>EGFR</b>		Y1172	Epidermal growth factor receptor-tyrosine kinase	-0.51	-0.96
<b>PDK1</b>		S241	3-Phosphoinositide-dependent protein-serine kinase 1	-0.51	-1.82
<b>JNK1/2/3</b>		T183 + Y185	Jun N-terminus protein-serine kinase (stress-activated protein kinase (SAPK)) 1/2/3	-0.52	-1.01
<b>EGFR</b>		T693	Epidermal growth factor receptor-tyrosine kinase	-0.52	-1.09
<b>KHS (MAP4K5)</b>		Pan-specific	Kinase homologous to SPS1/STE20 (MAP kinase kinase kinase protein-serine kinase 5 (MEKKK5))	-0.53	-1.15
<b>PKG1a</b>		Pan-specific	cGMP-dependent protein kinase 1, alpha isozyme	-0.54	-1.39
<b>PP2A/Ca</b>		Pan-specific	Protein-serine phosphatase 2A - catalytic subunit - alpha isoform	-0.54	-1.19
<b>pThr(RpAb)</b>		pThr	pThr(RpAb)	-0.54	-1.09
<b>Plk1</b>		Pan-specific	Polo-like protein-serine kinase 1	-0.54	-1.53
<b>PKCm (PKD)</b>		S910	Protein-serine kinase C mu (Protein kinase D)	-0.55	-1.09
<b>ZIPK</b>		Pan-specific	ZIP kinase (death associated protein-serine kinase 3 (DAPK3))	-0.55	-1.26
<b>PKCd</b>		T507	Protein-serine kinase C delta	-0.57	-1.75
<b>Ksr1</b>		Pan-specific	Protein-serine kinase suppressor of Ras 1	-0.57	-1.23
<b>Erk1 (MAPK3)+ Erk2 (MAPK1)</b>		Y204	Extracellular regulated protein-serine kinase 1 (p44 MAP kinase) + Extracellular regulated protein-serine kinase 2 (p42 MAP kinase)	-0.57	-1.17
<b>Ezrin</b>		Y353	cytovillin 2	-0.57	-1.15
<b>Ksr1</b>		Pan-specific	Protein-serine kinase suppressor of Ras 1	-0.58	-1.56
<b>PDGFRb</b>		Y716	Platelet-derived growth factor receptor kinase beta	-0.58	-1.09
<b>PKA R2a</b>		Pan-specific	cAMP-dependent protein-serine kinase regulatory type 2 subunit alpha	-0.58	-1.31
<b>PKBb (Akt2)</b>		Pan-specific	Protein-serine kinase B beta	-0.58	-1.21
<b>eIF4E</b>		S209	Eukaryotic translation initiation factor 4 (mRNA cap binding protein)	-0.58	-1.30
<b>PP1/Ca</b>		T320	Protein-serine phosphatase 1 - catalytic subunit - alpha isoform	-0.60	-1.57
<b>ZIPK</b>		Pan-specific	ZIP kinase (death associated protein-serine kinase 3 (DAPK3))	-0.61	-1.29
<b>IRAK4</b>		Pan-specific	Interleukin 1 receptor-associated kinase 4	-0.61	-2.05
<b>ErbB2 (HER2)</b>		Pan-specific	ErbB2 (Neu) receptor-tyrosine kinase	-0.61	-1.38
<b>eIF4G</b>		S1107	Eukaryotic translation initiation factor 4 gamma 1	-0.61	-1.02
<b>KDEL receptor 1</b>		Pan-specific	ER lumen protein retaining receptor 1	-0.63	-1.12
<b>Vrk1</b>		Pan-specific	Vaccinia related protein-serine kinase 1	-0.63	-1.41
<b>Caveolin 2</b>		Pan-specific	Caveolin 2	-0.63	-1.39
<b>MAPKAPK2a</b>		T334	Mitogen-activated protein kinase-activated protein kinase 2 alpha	-0.63	-1.23
<b>PDI</b>		Pan-specific	Protein disulfide-isomerase	-0.63	-1.00
<b>Jun</b>		S243	Jun proto-oncogene-encoded AP1 transcription factor	-0.63	-1.41
<b>PKCm (PKD)</b>		Pan-specific	Protein-serine kinase C mu (Protein kinase D)	-0.63	-1.37
<b>EGFR</b>		Y1172	Epidermal growth factor receptor-tyrosine kinase	-0.64	-1.21
<b>PKCm (PKD)</b>		S910	Protein-serine kinase C mu (Protein kinase D)	-0.64	-1.66
<b>hHR23B</b>		Pan-specific	UV excision repair protein RAD23 homolog B	-0.64	-1.28
<b>EGFR</b>		Y1092	Epidermal growth factor receptor-tyrosine kinase	-0.64	-1.24
<b>FAK</b>		S722	Focal adhesion protein-tyrosine kinase	-0.65	-1.20
<b>ErbB2 (HER2)</b>		Pan-specific	ErbB2 (Neu) receptor-tyrosine kinase	-0.65	-1.06
<b>CASP9</b>		Pan-specific	Caspase 9 (ICE-like apoptotic protease 6 (ICE-LAP6), Mch6, APAF3)	-0.66	-1.71
<b>Kit</b>		Y936	Kit/Steel factor receptor-tyrosine kinase	-0.66	-1.23
<b>Tyk2</b>		Pan-specific	Protein-tyrosine kinase 2 (Jak-related)	-0.66	-1.27
<b>FAK</b>		S722	Focal adhesion protein-tyrosine kinase	-0.67	-1.24
<b>Lck</b>		Pan-specific	Lymphocyte-specific protein-tyrosine kinase	-0.68	-1.22
<b>PAK1</b>		T212	p21-activated kinase 1 (alpha) (serine/threonine-protein kinase PAK 1)	-0.69	-1.33
<b>eIF2a</b>		S52	Eukaryotic translation initiation factor 2 alpha	-0.69	-1.35
<b>PKCb2</b>		T642	Protein-serine kinase C beta 2	-0.69	-1.34
<b>PLCg1</b>		Y771	1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-1	-0.69	-1.41
<b>PKCd</b>		S664	Protein-serine kinase C delta	-0.70	-1.37
<b>PKCg</b>		Pan-specific	Protein-serine kinase C gamma	-0.70	-1.29
<b>Lck</b>		Y192	Lymphocyte-specific protein-tyrosine kinase	-0.71	-1.21
<b>Jun</b>		S73	Jun proto-oncogene-encoded AP1 transcription factor	-0.71	-1.15
<b>MAPKAPK2a</b>		T334	Mitogen-activated protein kinase-activated protein kinase 2 alpha	-0.71	-1.66
<b>PKCh</b>		T655	Protein-serine kinase C eta	-0.71	-1.35
<b>MAPKAPK2</b>		T222	Mitogen-activated protein kinase-activated protein kinase 2	-0.71	-1.36
<b>pThr(MmAb)</b>		pThr	pThr(MmAb)	-0.72	-1.22
<b>4G10</b>		pTyr	4G10	-0.72	-1.38
<b>PKCe</b>		Pan-specific	Protein-serine kinase C epsilon	-0.73	-1.43
<b>Lck</b>		Y394	Lymphocyte-specific protein-tyrosine kinase	-0.73	-1.56
<b>Tyk2</b>		Pan-specific	Protein-tyrosine kinase 2 (Jak-related)	-0.73	-1.37
<b>PKC/i</b>		Pan-specific	Protein-serine kinase C lambda/iota	-0.73	-1.50
<b>Paxillin 1</b>		Y118	Paxillin 1	-0.74	-1.26
<b>Lck</b>		S158	Lymphocyte-specific protein-tyrosine kinase	-0.74	-1.22
<b>PKCd</b>		S645	Protein-serine kinase C delta	-0.74	-1.60
<b>LIMK1</b>		Y507+T508	LIM domain kinase 1	-0.75	-1.36
<b>Tyrosine Hydroxylase</b>		S18	Tyrosine hydroxylase isoform a	-0.76	-1.77
<b>PKCq</b>		S676	Protein-serine kinase C theta	-0.77	-1.69
<b>Lyn</b>		Y508	Yes-related protein-tyrosine kinase	-0.77	-1.96
<b>ZAP70/Syk</b>		Y319/Y352	Zeta-chain (TCR) associated protein-tyrosine kinase, 70 kDa/Spleen protein-tyrosine kinase	-0.77	-2.07

WIP1	Pan-specific	Protein phosphatase 1D	-0.77	-1.59
PKCq	Pan-specific	Protein-serine kinase C theta	-0.78	-1.68
PKCq	S695	Protein-serine kinase C theta	-0.78	-1.69
PKG1	Pan-specific	Protein-serine kinase G1 (cGMP-dependent protein kinase)	-0.78	-1.71
Lck	Pan-specific	Lymphocyte-specific protein-tyrosine kinase	-0.79	-1.70
LIMK1	Pan-specific	LIM domain kinase 1	-0.79	-1.65
PKCe	Pan-specific	Protein-serine kinase C epsilon	-0.79	-1.57
Lck	Y505	Lymphocyte-specific protein-tyrosine kinase	-0.80	-1.57
PKCg	T514	Protein-serine kinase C gamma	-0.80	-1.34
PKR1	T446	Double-stranded RNA-dependent protein-serine kinase (EIF2AK2)	-0.80	-1.73
PARP1	Pan-specific	Poly [ADP-ribose] polymerase 1 (ADPRT)	-0.81	-1.75
PLCg1	Y783	1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-1	-0.82	-1.76
Paxillin 1	Y31	Paxillin 1	-0.82	-1.59
p107	Pan-specific	Retinoblastoma (Rb) protein-related p107 (PRB1)	-0.84	-1.57
eIF4E	Pan-specific	Eukaryotic translation initiation factor 4 (mRNA cap binding protein)	-0.84	-1.83
PKCg	T514	Protein-serine kinase C gamma	-0.85	-1.51
MDM2	S166	double minute 2	-0.86	-1.67
LAR	Pan-specific	LCA antigen-related (LAR) receptor tyrosine phosphatase	-0.86	-1.85
PKCm (PKD)	S738+S742	Protein-serine kinase C mu (Protein kinase D)	-0.87	-1.96
PLC R(PLCg2)	Y753	1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-2	-0.88	-1.93
MEK1 (MAP2K1)	Pan-specific	MAPK/ERK protein-serine kinase 1 (MKK1)	-0.88	-1.83
PKCg	T655	Protein-serine kinase C gamma	-0.90	-1.61
Paxillin 1	Pan-specific	Paxillin 1	-0.90	-2.10
PKCg	T674	Protein-serine kinase C gamma	-0.90	-1.77
Jun	S63	Jun proto-oncogene-encoded AP1 transcription factor	-0.91	-2.43
Erk1 (MAPK3)+ Erk2 (MAPK1)	Pan-specific	Extracellular regulated protein-serine kinase 1 (p44 MAP kinase) +Extracellular regulated protein-serine kinase 2 (p42 MAP kinase)	-0.91	-2.17
JNK2/3	Pan-specific	Jun N-terminus protein-serine kinase (stress-activated protein kinase (SAPKa/b)) 2/3	-0.91	-2.29
VEGF-C	Pan-specific	Vascular endothelial growth factor C	-0.91	-1.85
FAK	S732	Focal adhesion protein-tyrosine kinase	-0.91	-1.81
PKCb1	Pan-specific	Protein-serine kinase C beta 1	-0.91	-1.90
Wee1	Pan-specific	Wee1 protein-tyrosine kinase	-0.92	-2.00
PKA Ca/b	Pan-specific	cAMP-dependent protein-serine kinase catalytic subunit alpha/beta	-0.92	-2.05
PDGFRa	Y754	Platelet-derived growth factor receptor kinase alpha	-0.94	-1.74
VEGFR2 (KDR)	Y1059	Vascular endothelial growth factor receptor-tyrosine kinase 2 (KDR)	-0.99	-2.07
Vimentin	S34	Vimentin	-1.00	-2.16
PKCi/i	T564	Protein-serine kinase C lambda/iota	-1.01	-2.26
PED15 (PEA15)	S116	Phosphoprotein-enriched in diabetes/astrocytes 15	-1.01	-2.15
PI3K p85/p55	Y467/Y199	Phosphatidylinositol 3-kinase regulatory subunit alpha	-1.08	-3.17
PI3K p85/p55	Pan-specific	Phosphatidylinositol 3-kinase regulatory subunit alpha	-1.09	-2.56
VEGFR2 (KDR)	Y1214	Vascular endothelial growth factor receptor-tyrosine kinase 2 (KDR)	-1.10	-2.57
Tyrosine Hydroxylase	S70	Tyrosine hydroxylase isoform a	-1.14	-2.95
PKCz/i	T410/T412	Protein-serine kinase C zeta/lambda	-1.20	-3.27
ZAP70	Pan-specific	Zeta-chain (TCR) associated protein-tyrosine kinase, 70 kDa	-1.23	-2.98
PDK1	Pan-specific	3-phosphoinositide-dependent protein-serine kinase 1	-1.25	-2.83
VHR	Pan-specific	Dual specificity protein phosphatase 3	-1.25	-3.03
PKBa (Akt1)	S473	Protein-serine kinase B alpha	-1.27	-3.00
MARCKS	S159+S163	Myristoylated alanine-rich protein kinase C substrate	-1.28	-3.31
Yes	Pan-specific	Yamaguchi sarcoma proto-oncogene-encoded tyrosine kinase	-1.33	-3.35

\*\*\* Z-score ratio cut-off value of +/- 0.95

**Supplementary Table 3: Annotated Changes in Total and Activated Protein Levels in WT vs.  $\Delta$ sagA GAS Infection**

Target Protein Name	Phospho Site (Human)	Normalized Fold Change	Z-ratio WT vs $\Delta$ sagA	Pathway or Function (summarized from uniprot.org protein function database)
<b>Regulation of Cell Survival and Growth Signaling</b>				
<b>AK2</b>	Pan-specific	1.14	1.00	Cellular energy homeostasis: catalyzes the reversible transfer of the terminal phosphate group between ATP and AMP.
<b>AMPK<math>\alpha</math>1/2</b>	T183	-0.31	-1.00	Cellular energy metabolism: catalytic subunit of AMP-activated protein kinase (AMPK), an energy sensor protein kinase that inhibits energy-consuming processes.
<b>Bcl-xS/L</b>	Pan-specific	1.04	1.14	Inhibits caspase activation: binds to and thereby blocks the release of CYC1 (caspase activator) from mitochondrial voltage-dependent anion channels (VDAC). Also regulates G2 checkpoint of cell cycle.
<b>CASP3</b>	Pan-specific	-0.41	-1.07	Apoptosis cascade: Cleaves and activates caspase-6, -7 and -9 and other apoptosis effectors.
<b>CASP7</b>	Pan-specific	1.28	1.23	Apoptosis cascade: activates PARP.
<b>CASP9</b>	Pan-specific	-0.66	-1.71	Apoptosis cascade: Activated through interaction with Apaf-1; cleaves and activates caspase-3 and cleaves PARP.
<b>Caveolin 2</b>	Pan-specific	-0.63	-1.39	May act as a scaffolding protein within caveolar membranes. Interacts with and regulates G-protein alpha subunit and also plays a role in targeting to lipid rafts and in driving caveolae formation.
<b>Csk</b>	Pan-specific	3.55	2.73	Non-receptor tyrosine-protein kinase that plays an important role in the regulation of cell growth, differentiation, migration and immune response. Phosphorylates tyrosine residues of Src-family kinases to inhibit activity.
<b>EGFR</b>	Y1197	-0.50	-1.10	Receptor tyrosine kinase that activates at least 4 major downstream signaling cascades including the RAS-RAF-MEK-ERK, PI3K-AKT, PLC $\gamma$ -PKC and STATs modules.
	Y1172	-0.64	-1.21	
	Y1092	-0.64	-1.24	
<b>ErbB2 (HER2)</b>	Pan-specific	-0.61	-1.38	Tyrosine kinase: participates in several cell surface receptor complexes and requires a coreceptor for ligand binding. Regulates organization of microtubules and plays a role in the regulation of protein synthesis and cell growth.
<b>Erk1/Erk2</b>	Pan-specific	-0.91	-2.17	MAPK serine/threonine kinase that mediates cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, and cytoskeletal rearrangements.
<b>FKHRL1 (FOXO3A)</b>	T32	2.19	1.76	Transcriptional activator: triggers apoptosis in the absence of survival factors or in response to oxidative stress. Post-transcriptionally regulates Myc following phosphorylation by MAPKAPK5. Negatively regulated by Akt1 (phosphorylated on Thr-32 and Ser-253). The dephosphorylated form triggers apoptosis in response to stress.
<b>FRS2</b>	Y348	1.10	1.31	Adapter protein that links activated FGR and NGF receptors to downstream signaling pathways. Plays a role in the activation of MAP kinases and in the phosphorylation of PIK3R1 (regulatory subunit of PI3K), in response to FGFR1 signaling. Negatively regulates signaling via SHC1.
<b>Fyn</b>	Pan-specific	1.44	1.54	Non-receptor tyrosine-protein kinase: plays a role in the regulation of cell growth and survival, cell adhesion, integrin-mediated signaling, cytoskeletal remodeling, cell motility, immune response and axon guidance.
<b>Gab1</b>	Y627	1.17	1.16	Adapter protein that plays a role in intracellular signaling cascades triggered by activated receptor-type kinases. Plays a role in FGFR1 signaling. Probably involved in signaling by the epidermal growth factor receptor (EGFR) and the insulin receptor (INSR).
<b>GNB2L1</b>	Pan-specific	1.15	1.12	Component of the 40S ribosomal subunit: represses translation by binding and stabilizing PKC, which promotes EIF6 phosphorylation. Inhibits SRC, LCK and YES1 kinase activity. Inhibits cell growth by prolonging the G0/G1 phase of the cell cycle. Promotes cell spreading and contact with the ECM. Promotes apoptosis by increasing oligomerization of BAX and disrupting the interaction of BAX with the anti-apoptotic factor BCL2L.
	Pan-specific	1.87	1.73	
<b>GSK3<math>\alpha</math></b>	Pan-specific	1.87	1.73	Constitutively active protein kinase that negatively regulates the hormonal control of glucose homeostasis, Wnt signaling and regulation of transcription factors and microtubules. Phosphorylates MCL1 to promote apoptosis in response to growth factor deprivation.
	Y279	0.97	1.05	
<b>IGF1Rb/IRb</b>	Y1161/Y1185	-0.36	-1.05	Receptor tyrosine kinase: mediates actions of insulin-like growth factor 1 (IGF1). Activates the PI3K-AKT/PKB pathway to inhibit apoptosis and promote protein synthesis and the Ras-MAPK pathway to increase cellular proliferation.
<b>IRS1</b>	S312	1.67	1.49	Mediates insulin responsive signaling. When phosphorylated by the insulin receptor binds specifically to various cellular proteins containing SH2 domains such as PI3K p85 or GRB2.
	Y1179	0.63	0.96	
<b>Kit</b>	Y936	-0.66	-1.23	Tyrosine-protein kinase that acts as cell-surface receptor for the cytokine KITLG/SCF and regulates cell survival and proliferation, hematopoiesis, stem cell maintenance, gametogenesis, mast cell development, migration and function, and melanogenesis.
<b>Ksr1</b>	Pan-specific	-0.58	-1.56	Location-regulated scaffolding protein connecting MEK to RAF.
<b>Lyn</b>	Y508	-0.77	-1.96	Non-receptor tyrosine-protein kinase: transmits signals from cell surface receptors and regulates innate and adaptive immune responses, hematopoiesis, responses to growth factors and cytokines, integrin signaling, and responses to DNA damage and genotoxic agents. Functions primarily as a negative regulator.
<b>MDM2</b>	S166	-0.86	-1.67	Negative regulator of apoptosis: E3 ubiquitin-protein ligase that mediates ubiquitination of p53/TP53, leading to its degradation by the proteasome. Also promotes proteasome-dependent ubiquitin-independent degradation of retinoblastoma RB1 protein.
<b>MEK1</b>	Pan-specific	-0.88	-1.83	Dual specificity protein kinase which participates in the MAPK/ERK cascade, responding to signals downstream of RAS and RAF1 activation.
<b>MKP2</b>	Pan-specific	1.58	1.51	Regulates mitogenic signal transduction by dephosphorylating both Thr and Tyr residues on MAP kinases ERK1 and ERK2.
<b>MST1</b>	Pan-specific	2.57	2.22	Stress-activated, pro-apoptotic kinase which, following caspase-cleavage, enters the nucleus and induces chromatin condensation followed by internucleosomal DNA fragmentation. Inhibits AKT1 signaling.
<b>Myc</b>	T58	1.08	1.20	Transcription factor: involved in promoting cell growth proliferation and recruits histone acetyltransferases.
<b>p53</b>	S392	-0.34	-1.16	Acts as a tumor suppressor gene; induces growth arrest or apoptosis depending on the physiological circumstances and cell type. Involved in cell cycle regulation by controlling inhibitors of cyclin-dependent kinases. Also activates oxidative stress-induced necrosis.
<b>PAK1</b>	T212	-0.69	-1.33	Protein kinase: involved in intracellular signaling pathways downstream of integrins and receptor-type kinases. Plays an important role in cytoskeleton dynamics, cell adhesion, migration, proliferation, apoptosis, mitosis, and vesicle-mediated transport processes. Can directly phosphorylate BAD and protects cells against apoptosis. Activity is inhibited in cells undergoing apoptosis.
<b>PDGFR<math>\alpha</math></b>	Y754	-0.94	-1.74	Tyrosine-protein kinase that acts as a cell-surface receptor for PDGFA, PDGFB and PDGFC and plays an essential role in the regulation of embryonic development, cell proliferation, survival and chemotaxis. Plays a role in platelet activation, secretion of agonists from platelet granules, and in thrombin-induced platelet aggregation. Mediates activation of the AKT1 signaling, MAPK/ERK pathway, and STAT family members.
<b>PDGFR<math>\beta</math></b>	Y716	-0.58	-1.09	Tyrosine-protein kinase that acts as cell-surface receptor for homodimeric PDGFB and PDGFD and for heterodimers formed by PDGFA and PDGFB, and plays an essential role in the regulation of embryonic development, cell proliferation, survival, differentiation, chemotaxis and migration. Activates AKT1 signaling via PI3K, MAPK1/ERK2 and/or MAPK3/ERK1 pathways, and activation of SRC family kinases.



PKD1	Pan-specific	-0.48	-1.42	Serine/threonine kinase which acts as a master kinase, targeting: AKT, RPS6Ks, protein kinase C, SGKs, p21-activated kinase-1 (PAK1), and protein kinase PKN. Plays a central role in the transduction of signals from insulin to downstream targets controlling cell proliferation and survival, as well as glucose and amino acid uptake and storage.
	S241	-0.51	-1.82	
	Pan-specific	-1.25	-2.83	
PED15	S116	-1.01	-2.15	Blocks Ras-mediated inhibition of integrin activation and modulates the ERK MAP kinase cascade.
PI3K p85/p55	Y467/Y199	-1.08	-3.17	Binds to activated (phosphorylated) protein-Tyr kinases, through its SH2 domain, and acts as an adapter, mediating the association of the p110 catalytic unit to the plasma membrane. Necessary for the insulin-stimulated increase in glucose uptake and glycogen synthesis in insulin-sensitive tissues. Plays an important role in signaling in response to FGFR1, FGFR2, FGFR3, FGFR4, KITLG/SCF, KIT, PDGFRA and PDGFRB, and ITGB2.
	Pan-specific	-1.09	-2.56	
PKA R2a	Pan-specific	-0.58	-1.31	Regulatory subunit of the cAMP-dependent protein kinases involved in cAMP signaling in cells. Type II regulatory chains mediate membrane association by binding to anchoring proteins, including the MAP2 kinase.
PKBa (Akt1)	S473	-1.27	-3.00	Serine/threonine-protein kinase that regulates many processes including metabolism, proliferation, cell survival, growth and angiogenesis. Responsible of the regulation of glucose uptake and storage of glucose in the form of glycogen. Mediates protein synthesis through mTORC1 signaling. Acts as an anti-apoptotic factor through regulation BAD, FOXO, p53, MAP3Ks and additional targets.
	T308	-0.49	-1.68	
PKBb (Akt2)	Pan-specific	-0.58	-1.21	
PKCb2	T642	-0.69	-1.34	Regulatory subunit of the cAMP-dependent protein kinases involved in cAMP signaling in cells. Type II regulatory chains mediate membrane association by binding to anchoring proteins, including the MAP2 kinase.
PKCd	S645	-0.74	-1.60	Calcium-independent, phospholipid- and diacylglycerol (DAG)-dependent serine/threonine-protein kinase that plays contrasting roles in cell death and cell survival by functioning as a pro-apoptotic protein during DNA damage-induced apoptosis, but acting as an anti-apoptotic protein during cytokine receptor-initiated cell death. It is required for oxygen radical production by NADPH oxidase and acts as positive or negative regulator in platelet functional responses.
PKCe	Pan-specific	-0.79	-1.57	Calcium-independent, phospholipid- and diacylglycerol (DAG)-dependent serine/threonine-protein kinase that plays essential roles in the regulation of multiple cellular processes linked to cytoskeletal proteins, such as cell adhesion, motility, migration and cell cycle, functions in neuron growth and ion channel regulation, and is involved in immune response, cancer cell invasion and regulation of apoptosis. May be involved in the regulation of the insulin-induced phosphorylation and activation of AKT1.
PKCh	T655	-0.71	-1.35	Calcium-independent, phospholipid- and diacylglycerol (DAG)-dependent serine/threonine-protein kinase that is involved in the regulation of cell differentiation in keratinocytes, mediates regulation of epithelial tight junction integrity, and prevents apoptosis. Interacts with FYN to induce keratinocyte growth arrest and differentiation. Can activate the mTOR pathway, the PI3K/AKT pathway and the ERK1-dependent phosphorylation of ELK1. Involved in protection from irradiation and DNA damage-induced apoptosis by preventing caspase-9 activation and ATF2 phosphorylation.
PKCi/i	T564	-1.01	-2.26	Calcium- and diacylglycerol-independent serine/ threonine-protein kinase that plays a general protective role against apoptotic stimuli, is involved in NF-kappa-B activation, cell survival, differentiation and polarity, and contributes to the regulation of microtubule dynamics in the early secretory pathway. May function downstream of phosphatidylinositol 3-kinase (PI3K) and PDK1 in the promotion of cell survival by phosphorylating and inhibiting the pro-apoptotic factor BAD.
PKCq	S695	-0.78	-1.69	Phosphorylates PDKP1 at 'Ser-504' and 'Ser-532' and negatively regulates its ability to phosphorylate PKB/AKT1.
PKCz/l	T410/T412	-1.20	-3.27	Calcium- and diacylglycerol-independent serine/threonine-protein kinase that functions in phosphatidylinositol 3-kinase (PI3K) pathway and mitogen-activated protein (MAP) kinase cascade, and is involved in NF-kappa-B activation, mitogenic signaling, cell proliferation, cell polarity, inflammatory response and maintenance of long-term potentiation (LTP).
PKM2	Pan-specific	-0.42	-1.03	Glycolytic enzyme that catalyzes the transfer of a phosphoryl group from phosphoenolpyruvate (PEP) to ADP, generating ATP.
PLC R(PLCg2)	Y753	-0.88	-1.93	The production of the second messenger molecules diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) is mediated by activated phosphatidylinositol-specific phospholipase C enzymes.
PLCg1	Y771	-0.69	-1.41	Mediates the production of the second messenger molecules diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). Plays an important role in the regulation of intracellular signaling cascades. Becomes activated in response to ligand-mediated activation of receptor-type tyrosine kinases, such as PDGFRA, PDGFRB, FGFR1, FGFR2, FGFR3 and FGFR4. Plays a role in actin reorganization and cell migration.
	Y783	-0.82	-1.76	
PRK2 (PKN2)	Pan-specific	0.90	1.04	PKC-related serine/threonine-protein kinase and Rho/Rac effector protein that regulates cell cycle progression, actin cytoskeleton assembly, cell migration, cell adhesion, tumor cell invasion and transcription activation signaling processes.
PTEN	S380+T382+T383	1.28	1.28	Acts as a dual-specificity protein and lipid phosphatase, dephosphorylating tyrosine-, serine- and threonine-phosphorylated proteins as well as removing the phosphate in the D3 position of the inositol ring from PI 3,4,5-trisphosphate, PI 3,4-diphosphate, PI 3-phosphate and inositol 1,3,4,5-tetrakisphosphate. Antagonizes the PI3K-AKT/PKB signaling pathway thereby modulating cell cycle progression and cell survival. Dephosphorylates tyrosine-phosphorylated focal adhesion kinase and inhibits cell migration and integrin-mediated cell spreading and focal adhesion formation. Plays a role in mitochondrial energetic metabolism by promoting COX activity and ATP production.
	S380+T382+T383	1.17	1.18	
pThr(MmAb)	pThr	-0.72	-1.22	Phosphorylation site for serine-threonine kinases
pThr(RpAb)	pThr	-0.54	-1.09	
RSK1/2	S380/S386	4.79	2.59	Serine/threonine-protein kinase that acts downstream of ERK (MAPK1/ERK2 and MAPK3/ERK1) signaling and mediates mitogenic and stress-induced activation of the transcription factors CREB1, ETV1/ER81 and NR4A1/NUR77, regulates translation through RPS6 and EIF4B phosphorylation, and mediates cellular proliferation, survival, and differentiation by modulating mTOR signaling and repressing pro-apoptotic function of BAD and DAPK1.
RSK1/3	T359+S363/ T356+S360	2.49	1.76	
S6K	S411	1.99	1.89	Serine/threonine-protein kinase that acts downstream of mTOR signaling in response to growth factors and nutrients to promote cell proliferation, cell growth and cell cycle progression. Regulates protein synthesis through phosphorylation of EIF4B, RPS6 and EEF2K, and contributes to cell survival by repressing the pro-apoptotic function of BAD. Also plays a role in feedback regulation of mTORC and AKT1 by phosphorylating RICTOR.
S6Kb1	T412	2.93	2.07	
S6Kb2	Pan-specific	1.50	1.45	
Shc1	Y349	2.54	2.12	Signaling adapter that couples activated growth factor receptors to signaling pathways. Participates in signaling initiated by activated KIT and KITLG/SCF. Acts as a downstream target of p53 and is indispensable for the ability of stress-activated p53 to induce elevation of intracellular oxidants, cytochrome c release and apoptosis.
	Y349+Y350	0.89	1.21	
Smac/DIABLO	Pan-specific	1.64	1.61	Promotes apoptosis by activating caspases in the cytochrome c/Apaf-1/caspase-9 pathway. Acts by opposing the inhibitory activity of inhibitor of apoptosis proteins (IAP).
Smad1/5/8	S463+S465/S463 +S465/S465+S467	3.78	2.40	Transcriptional modulator activated by BMP (bone morphogenetic proteins) type 1 receptor kinase. SMAD1/OAZ1/PSMB4 complex mediates the degradation of the CREBBP/EP300 repressor SNIP1.
Smad2	T200	2.21	1.97	Receptor-regulated SMAD (R-SMAD) that is an intracellular signal transducer and transcriptional modulator activated by TGF-beta and activin type 1 receptor kinases. Binds the TRE element in the promoter region of many genes that are regulated by TGF-beta and, on formation of the SMAD2/SMAD4 complex, activates transcription. Positively regulates PDK1 kinase activity by stimulating its dissociation from the 14-3-3 protein YWHAQ.
	S467	2.01	1.92	
Smad2/3	Pan-specific	2.10	1.82	
SPHK1	Pan-specific	1.21	1.13	Catalyzes the phosphorylation of sphingosine to form sphingosine 1-phosphate (SPP), a lipid mediator with both intra- and extracellular functions. Also acts on D-erythro-sphingosine and to a lesser extent sphingosine, but not other lipids, such as D,L-threo-dihydrosphingosine, N,N-dimethylsphingosine, diacylglycerol, ceramide, or phosphatidylinositol.

<b>SPHK2</b>	Pan-specific	1.00	0.96	Catalyzes the phosphorylation of sphingosine to form sphingosine 1-phosphate (SPP), a lipid mediator with both intra- and extracellular functions. Also acts on D-erythro-dihydrosphingosine, D-erythro-sphingosine and L-threo-dihydrosphingosine. Binds phosphoinositides.
<b>VHR</b>	Pan-specific	-1.25	-3.03	Shows activity both for tyrosine-protein phosphate and serine-protein phosphate, but displays a strong preference toward phosphotyrosines. Specifically dephosphorylates and inactivates ERK1 and ERK2.
<b>Yes</b>	Pan-specific	-1.33	-3.35	Non-receptor protein tyrosine kinase: involved in the regulation of cell growth and survival, apoptosis, cell-cell adhesion, cytoskeleton remodeling, and differentiation. Stimulation by receptor tyrosine kinases (RTKs) including EGRF, PDGFR, CSF1R and FGFR leads to recruitment of YES1 to the phosphorylated receptor, and activation and phosphorylation of downstream substrates. Upon EGFR activation, promotes epithelial tight junction assembly.
<b>ZIPK</b>	Pan-specific	-0.61	-1.29	Serine/threonine kinase which is involved in the regulation of apoptosis, autophagy, transcription, translation, actin cytoskeleton reorganization, cell motility, smooth muscle contraction, and mitosis, particularly cytokinesis. Regulates type I apoptotic and type II autophagic cell death. Positively regulates STAT3 and Wnt/beta-catenin signaling.
<b>Stress and Inflammatory Signaling</b>				
<b>CASP1</b>	Pan-specific	-0.45	-1.23	Thiol protease that cleaves IL-1 $\beta$ to release the mature cytokine, which is involved in a variety of inflammatory processes. Important for defense against pathogens. Can also promote cell death, and cleaved caspase is associated with pyroptosis.
<b>COX2</b>	Pan-specific	2.85	2.25	Converts arachidonate to prostaglandin H2 (PGH2), a committed step in prostanoid synthesis and pro-inflammatory cascades.
<b>Crystallin aB</b>	Pan-specific	2.48	2.31	Has chaperone-like activity, preventing aggregation of various proteins under a wide range of stress conditions.
<b>Csk</b>	Pan-specific	3.55	2.73	Non-receptor tyrosine-protein kinase that plays an important role in the regulation of cell growth, differentiation, migration and immune response. Phosphorylates tyrosine residues of Src-family kinases to inhibit activity.
<b>GroEL</b>	Pan-specific	1.66	1.71	Implicated in mitochondrial protein import and macromolecular assembly; facilitates correct folding of proteins.
<b>Hsp27</b>	S82	8.36	3.71	Involved in stress resistance and actin organization. Can be activated by MAPK p38 signaling in response to a variety of stressors including temperature, osmotic stress, and oxidative stress.
<b>Hsp40</b>	Pan-specific	1.25	1.09	Interacts with HSP70 and can stimulate its ATPase activity. Stimulates the association between HSC70 and HIP.
<b>Hsp90a/b</b>	Pan-specific	2.50	2.01	Molecular chaperone that promotes the maturation, structural maintenance and proper regulation of specific target proteins involved for instance in cell cycle control and signal transduction.
<b>IkB<math>\alpha</math></b>	Pan-specific	6.97	3.55	Inhibits the activity of dimeric NF-kappa-B/REL complexes by trapping REL dimers in the cytoplasm. On cellular stimulation by immune and proinflammatory responses, becomes phosphorylated promoting ubiquitination and degradation, enabling the dimeric REL $\alpha$ to translocate to the nucleus and activate transcription. Also a transcriptional target of NFkB as part of a negative feedback loop.
<b>IKK<math>\alpha</math></b>	S180	1.58	0.99	Activator of NFkB signaling pathway: serine kinase that is a subunit of the IKK complex. Phosphorylates inhibitors of NFkB on serine residues to initiate their polyubiquitination and subsequent degradation by the proteasome. In non-canonical NFkB signaling, the MAP3K14-activated CHUK/IKKA homodimer phosphorylates NFkB2/p100 associated with RelB to induce proteolytic processing and subsequent NFkB activation.
<b>IRAK2</b>	Pan-specific	1.36	1.26	Binds to the IL-1 type I receptor following IL-1 engagement, triggering intracellular signaling cascades leading to transcriptional up-regulation and mRNA stabilization.
<b>IRAK4</b>	Pan-specific	-0.61	-2.05	Serine/threonine-protein kinase: plays a role in initiating innate immune response against pathogens. Involved in Toll-like receptor (TLR) and IL-1R signaling pathways and is rapidly recruited by MYD88 upon TLR activation along with IRAK2. Activates IRAK1 and participates in the IRAK1-MAP3K7/TAK1-TRAF6 complex and the NEMO-IKKA-IKKB complex leading to NFkB activation. Also regulates NADPH oxidase activation during microbial infections.
<b>JAK1</b>	Y1034	0.98	0.95	Non-receptor tyrosine kinase: involved in the IFN-alpha/beta/gamma signaling pathway. Kinase partner for the interleukin (IL)-2 receptor.
<b>JNK1</b>	Pan-specific	2.31	2.05	MAPK family serine/threonine-protein kinase involved in regulation of cell proliferation, differentiation, migration, transformation and programmed cell death. Responds to proinflammatory cytokines or physical stress and phosphorylates a number of transcription factors, primarily AP-1 family members (i.e. JUN, JDP2 and ATF2). Promotes stressed cell apoptosis by phosphorylating key regulatory factors including p53/TP53 and Yes-associates protein YAP1. Mediates starvation-induced BCL2 phosphorylation and dissociation from BECN1 to promote autophagy.
<b>JNK1/2/3</b>	Pan-specific	1.76	1.40	MAPK family serine/threonine-protein kinase involved in cell proliferation, differentiation, migration, transformation and programmed cell death. Extracellular stimuli such as proinflammatory cytokines or physical stress stimulate the stress-activated protein kinase/c-Jun N-terminal kinase (SAP/JNK) signaling pathway. Activates AP-1 transcription factors such as JUN and ATF2. In response to oxidative or ribotoxic stresses, inhibits rRNA synthesis. Promotes stressed cell apoptosis by phosphorylating key regulatory factors including TP53 and YAP1. Plays an important role in osmotic stress-induced epithelial tight-junctions disruption. Also inhibits the canonical Wnt signaling pathway.
<b>JNK2/3</b>	Pan-specific	-0.91	-2.29	MAPK family serine/threonine-protein kinase involved in cell proliferation, differentiation, migration, transformation and programmed cell death. Extracellular stimuli such as proinflammatory cytokines or physical stress stimulate the stress-activated protein kinase/c-Jun N-terminal kinase (SAP/JNK) signaling pathway. Activates AP-1 transcription factors such as JUN and ATF2. In response to oxidative or ribotoxic stresses, inhibits rRNA synthesis. Promotes stressed cell apoptosis by phosphorylating key regulatory factors including TP53 and YAP1. Plays an important role in osmotic stress-induced epithelial tight-junctions disruption. Also inhibits the canonical Wnt signaling pathway.
<b>Jun</b>	S63	-0.91	-2.43	Transcription factor: promotes activity of NR5A1 when phosphorylated by HIPK3. Activation leads to increased steroidogenic gene expression upon cAMP signaling pathway stimulation.
<b>MAPKAPK2</b>	T222	-0.71	-1.36	Stress-activated serine/threonine-protein kinase involved in cytokines production, endocytosis, reorganization of the cytoskeleton, cell migration, cell cycle control, chromatin remodeling, DNA damage response and transcriptional regulation. Following stress, it is phosphorylated and activated by MAP kinase p38-alpha/MAPK14. Phosphorylates HSP27/HSPB1 in response to stress. Involved in inflammatory response by regulating tumor necrosis factor (TNF) and IL6 production post-transcriptionally. Also involved in late G2/M checkpoint following DNA damage.
<b>MAPKAPK2a</b>	T334	-0.71	-1.66	Stress-activated serine/threonine-protein kinase involved in cytokines production, endocytosis, reorganization of the cytoskeleton, cell migration, cell cycle control, chromatin remodeling, DNA damage response and transcriptional regulation. Following stress, it is phosphorylated and activated by MAP kinase p38-alpha/MAPK14. Phosphorylates HSP27/HSPB1 in response to stress. Involved in inflammatory response by regulating tumor necrosis factor (TNF) and IL6 production post-transcriptionally. Also involved in late G2/M checkpoint following DNA damage.
<b>MEK4</b>	Pan-specific	1.40	1.40	MAPK family dual specificity protein kinase which acts upstream of JNK signaling pathway. With MAP2K7/MKK7, it directly activates JNK. The MKK/JNK signaling pathway regulates the mitochondrial death signaling pathway. MAP2K4/MKK4 can also activate p38 MAPKs (MAPK11, MAPK12, MAPK13 and MAPK14).
<b>MEK6</b>	Pan-specific	1.36	1.31	MAPK family dual specificity protein kinase which, with MAP3K3/MKK3, activates MAPK p38 and plays an important role in the regulation of cellular responses to cytokines and all kinds of stresses. The p38 MAP kinase signal transduction pathway leads to direct activation of numerous transcription factors, including NFkB and STATs. Also crucial for IL-6-induced SOCS3 expression and for IFNG-dependent gene transcription.
<b>MEKK2</b>	Pan-specific	1.66	1.71	MAPK family: regulates the JNK and ERK5 pathways by phosphorylating and activating MAP2K5 and MAP2K7.
<b>Mnk1</b>	T250+T255	5.09	3.34	Plays a role in the response to environmental stress and cytokines. Regulates translation by phosphorylating EIF4E to increase its affinity to the 7-methylguanosine-containing mRNA cap.
<b>Msk1</b>	S376	1.58	1.32	Serine/threonine-protein kinase required for the mitogen or stress-induced phosphorylation of CREB1, ATF1, STAT3, ETV1/ER81, and RELA transcription factors.
<b>PKA Ca/b</b>	Pan-specific	-0.92	-2.05	Phosphorylates a large number of substrates in the cytoplasm and the nucleus including CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA and VASP. Involved in the regulation of platelets in response to thrombin and collagen. Negatively regulates tight junctions (TJs) via CLDN3 phosphorylation.
<b>PKCa/b2</b>	T638/T641	1.63	1.05	Phosphorylates a large number of substrates in the cytoplasm and the nucleus including CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA and VASP. Involved in the regulation of platelets in response to thrombin and collagen. Negatively regulates tight junctions (TJs) via CLDN3 phosphorylation.
<b>PKCm (PKD)</b>	S738+S742	-0.87	-1.96	Serine/threonine-protein kinase: converts diacylglycerol (DAG) signals into prolonged physiological effects downstream of PKC and is involved in the regulation of MAPK8/JNK1 and Ras signaling, Golgi membrane integrity and trafficking, cell survival through NFkB activation, cell migration, cell differentiation by mediating HDAC7 nuclear export, cell proliferation via MAPK13 (ERK1/2) signaling, and plays a role in cardiac hypertrophy, VEGFA-induced angiogenesis, genotoxic-induced apoptosis and flagellin-stimulated inflammatory response. Under oxidative stress, is phosphorylated by SRC-ABL1 to promote cell survival by activating the IKK complex. Plays a role in the proliferative response induced by low calcium in keratinocytes via ERK1/2 pathway. Participates in TLR5 signaling to activate p38 and inflammatory cytokine production.
<b>RelB</b>	Pan-specific	1.15	1.31	NFkB is a pleiotropic transcription factor which is present in almost all cell types and is involved in many biological processes such as inflammation, immunity, differentiation, cell growth, tumorigenesis and apoptosis.

<b>Smad1/5/8</b>	S463+S465/S463+S465/S465+S467	3.78	2.40	Transcriptional modulator activated by BMP (bone morphogenetic proteins) type 1 receptor kinase. SMAD1 is a receptor-regulated SMAD (R-SMAD). SMAD1/OAZ1/PSMB4 complex mediates the degradation of the CREBBP/EP300 repressor SNIP1.
<b>Smad2</b>	T200	2.21	1.97	Receptor-regulated SMAD (R-SMAD) that is an intracellular signal transducer and transcriptional modulator activated by TGF- $\beta$ and activin type 1 receptor kinases. Binds the TRE element in the promoter region of many genes that are regulated by TGF- $\beta$ and, on formation of the SMAD2/SMAD4 complex, activates transcription.
	S467	2.01	1.92	
<b>Smad2/3</b>	Pan-specific	2.10	1.82	
<b>SOCS4</b>	Pan-specific	2.21	2.06	SOCS family proteins form part of a classical negative feedback system that regulates cytokine signal transduction. Inhibits EGF signaling by mediating the degradation of the Tyr-phosphorylated EGF receptor/EGFR.
<b>SOD (Cu/Zn)</b>	Pan-specific	1.08	1.12	Destroys radicals which are normally produced within the cells and which are toxic to biological systems.
<b>SOD (Mn)</b>	Pan-specific	1.65	1.48	Destroys superoxide anion radicals which are normally produced within the cells and which are toxic to biological systems.
<b>SODD</b>	Pan-specific	1.32	1.36	Enzyme with a broad specificity. Negatively regulates TGF- $\beta$ signaling through dephosphorylating SMAD2 and SMAD3, resulting in their dissociation from SMAD4, nuclear export of the SMADs and termination of the TGF- $\beta$ -mediated signaling. Terminates TNF- $\alpha$ -mediated NF $\kappa$ B activation by dephosphorylating IKK $\beta$ /IKK $\gamma$ .
<b>Src</b>	Y530	1.71	1.70	Non-receptor protein tyrosine kinase: activated following engagement of many different classes of cellular receptors (i.e. immune response receptors, integrins and other adhesion receptors, receptor protein tyrosine kinases, G protein-coupled receptors and cytokine receptors). Participates in signaling pathways that control a diverse spectrum of biological activities including gene transcription, immune response, cell adhesion, cell cycle progression, apoptosis, migration, and transformation. Also plays a role in EGF-mediated calcium-activated chloride channel activation.
	Pan-specific	1.28	1.33	
	Pan-specific	1.56	1.30	
	Pan-specific	1.36	1.24	
<b>STAT1a</b>	Pan-specific	1.25	1.45	Signal transducer and transcription activator that mediates cellular responses to interferons (IFNs), cytokine KITLG/SCF as well as other cytokines growth factors. Following type I IFN (IFN-alpha and IFN-beta) binding to cell surface receptors, signaling via protein kinases leads to activation of Jak kinases (TYK2 and JAK1) and to tyrosine phosphorylation of STAT1 and STAT2. Becomes activated in response to KITLG/SCF and KIT signaling as well as FGFR1, FGFR2, FGFR3 and FGFR4.
	Y701	3.10	1.74	
<b>STAT2</b>	Y690	1.65	1.40	
<b>STAT3</b>	Y705	2.87	1.92	Signal transducer and transcriptional activator that mediates cellular responses to interleukins, KITLG/SCF and other growth factors. Mediates responses to activated FGFR1, FGFR2, FGFR3 and FGFR4. Binds to the interleukin-6 (IL-6)-responsive elements identified in the promoters of various acute-phase protein genes. Cytoplasmic STAT3 represses macroautophagy and aids in host defense against bacteria.
	S727	2.58	2.03	
<b>STAT5A</b>	S780	1.60	1.44	Mediates cellular responses to the cytokine KITLG/SCF, ERBB4, and FGFR1, FGFR2, FGFR3 and FGFR4. Binds to the GAS element and activates PRL-induced transcription.
	Y694	3.20	2.08	
<b>Tyk2</b>	Pan-specific	-0.73	-1.37	Involved in intracellular signal transduction by initiating type I IFN signaling. Phosphorylates the interferon-alpha/beta receptor alpha chain.
<b>Cytoskeletal Rearrangements and Cell to Cell Contact Proteins</b>				
<b>Bcr</b>	Y177	2.42	2.03	GTPase-activating protein for RAC1 and CDC42. Promotes the exchange of RAC or CDC42-bound GDP by GTP, thereby activating them. Displays serine/threonine kinase activity.
<b>Cofilin 1</b>	Pan-specific	2.17	1.84	Regulates actin cytoskeleton dynamics: binds to F-actin and exhibits pH-sensitive F-actin depolymerizing activity. Aids in regulation of cell cycle progression and cytokinesis and plays a role in the regulation of cell morphology.
<b>Cofilin 2</b>	S3	0.79	0.99	Controls reversibly actin polymerization and depolymerization in a pH-sensitive manner. It has the ability to bind G- and F-actin in a 1:1 ratio of cofilin to actin. It is the major component of intranuclear and cytoplasmic actin rods.
<b>Connexin 43</b>	S368	1.12	1.21	Gap junction protein that interacts with transmembrane channels to regulate diffusion of materials of low MW from one cell to a neighboring cell.
<b>EFNA5</b>	Pan-specific	-0.42	-0.98	Cell surface GPI-bound ligand for Eph receptors, a family of RTKs which are crucial for migration, repulsion and adhesion during neuronal, vascular and epithelial development. Aids in regulation of signaling through Fyn to control cell-cell adhesion and cytoskeletal organization.
<b>EFNB2</b>	Y316	-0.41	-1.08	Cell surface GPI-bound ligand for Eph receptors, a family of RTKs which are crucial for migration, repulsion and adhesion during neuronal, vascular and epithelial development. Aids in regulation of signaling through Fyn to control cell-cell adhesion and cytoskeletal organization. Together with EPHB4 plays a central role in heart morphogenesis and angiogenesis through regulation of cell adhesion and cell migration.
<b>Ezrin</b>	Y353	-0.57	-1.15	Involved in connections of major cytoskeletal structures to the plasma membrane. In epithelial cells, required for the formation of microvilli and membrane ruffles on the apical pole. Along with PLEKHG6, required for normal macropinocytosis.
<b>FAK</b>	Y576	5.48	3.01	Non-receptor protein-tyrosine kinase: regulates cell migration, adhesion, spreading, reorganization of the actin cytoskeleton, formation and disassembly of focal adhesions and cell protrusions, cell cycle progression, cell proliferation and apoptosis. Functions in integrin signal transduction and in signaling downstream of growth factor receptors, G-protein coupled receptors (GPCR), EPHA2, netrin receptors and LDL receptors. Forms complexes with SRC and SRC family members upon activation to allow binding of additional scaffold proteins, effectors and substrates. Promotes PI3K/AKT1 and ERK1/2 signaling cascades. Also promotes activation of GEFs and GAPs to regulate Rho family GTPases. Regulates cell death via recruitment of the ubiquitin ligase MDM2 to P53/TP53 in the nucleus. Phosphorylates SRC, ACTN1, ARHGEF7, GRB7, RET, and WASL. Promotes phosphorylation of PXN, STAT1, BCAR1, GIT2, SHC1, BMX and PIK3R1. (Y576 = activating site)
	S722	-0.65	-1.20	
	S722	-0.67	-1.24	
	S732	-0.91	-1.81	
<b>Fyn</b>	Pan-specific	1.44	1.54	Non-receptor tyrosine-protein kinase: plays a role in regulation of cell growth and survival, cell adhesion, integrin-mediated signaling, cytoskeletal remodeling, cell motility, immune response and axon guidance. Activated by PKA and associates with PTK2/FAK1 and catenins to regulate focal adhesions and with WAS, MAP2 and MAPT to regulate cytoskeletal remodeling.
<b>GNB2L1</b>	Pan-specific	1.15	1.12	Component of the 40S ribosomal subunit involved in translational repression. Also involved in the recruitment, assembly and/or regulation of a variety of signaling molecules including PKC, SRC kinases (SRC, LCK and YES1), RhoA, and IGF1R-dependent signaling proteins. Plays a role in cell spreading and contact with the extracellular matrix. Regulates cell surface expression of ADAM12 and some GPCRs such as TBXA2R.
<b>Huntingtin</b>	S421	2.56	2.19	May play a role in microtubule-mediated transport or vesicle function.
<b>ILK1</b>	Pan-specific	1.19	1.22	Receptor-proximal protein kinase regulating integrin-mediated signal transduction. Also participates in focal adhesion complexes and growth factor responsive signaling. Plays a role in the regulation of cell architecture and anchorage-dependent growth in epithelial cells.
<b>KDEL receptor 1</b>	Pan-specific	-0.63	-1.12	Endoplasmic reticulum and Golgi vesicular trafficking protein: required for the retention of luminal ER resident proteins via vesicular recycling. Recognizes the C-terminal K-D-E-L motif. Retrograde trafficking of KDEL receptor-ligand complexes is mediated by COPI-coated transport intermediates.
<b>LAR</b>	Pan-specific	-0.86	-1.85	Possible cell adhesion receptor that has intrinsic protein tyrosine phosphatase activity (PTPase). Also dephosphorylates EPHA2 to regulate its activity.
<b>LIMK1</b>	Y507+Y508	-0.75	-1.36	Serine/threonine-protein kinase: plays a role in the regulation of actin filament dynamics. Acts downstream of Rho family GTPase signal transduction pathways. Activated by upstream kinases including ROCK1, PAK1 and PAK4, which phosphorylate LIMK1. Stabilizes the actin cytoskeleton by inactivating the actin binding/depolymerizing factors cofilin-1/CFIL1, cofilin-2/CFIL2 and destrin/DSTN, thereby preventing the cleavage of filamentous actin (F-actin). Also phosphorylates PPPP to promote microtubule disassembly.
<b>MARCKS</b>	S159+S163	-1.28	-3.31	The most prominent cellular substrate for protein kinase C. This protein binds calmodulin, actin, and synapsin. MARCKS is a filamentous (F) actin cross-linking protein.

<b>PAK1</b>	T212	-0.69	-1.33	Protein kinase involved in intracellular signaling pathways downstream of integrins and receptor-type kinases that plays an important role in cytoskeleton dynamics, focal adhesions, migration, proliferation, apoptosis, mitosis, and in vesicle-mediated transport processes. Activated by CDC42 and RAC1. Functions as GTPase effector that links the Rho-related GTPases CDC42 and RAC1 to the JNK MAP kinase pathway. Interacts with the tubulin chaperone TBCB to regulate organization of the tubulin cytoskeleton and is required for phosphorylation of LIMK1 and cofilin (CFL1). Also plays a role in chemokine uptake and degradation.
<b>Paxillin 1</b>	Y118	-0.74	-1.26	Cytoskeletal protein involved in actin-membrane attachment at sites of cell adhesion to the extracellular matrix (focal adhesion).
	Y31	-0.82	-1.59	
	Pan-specific	-0.90	-2.10	
<b>PKCe</b>	Pan-specific	-0.79	-1.57	Calcium-independent, phospholipid- and diacylglycerol (DAG)-dependent serine/threonine-protein kinase that plays essential roles in the regulation of multiple cellular processes linked to cytoskeletal proteins, such as cell adhesion, motility, migration and cell cycle, functions in neuron growth and ion channel regulation, and is involved in immune response, cancer cell invasion and regulation of apoptosis. May be involved in the regulation of the insulin-induced phosphorylation and activation of AKT1.
<b>PKCh</b>	T655	-0.71	-1.35	Calcium-independent, phospholipid- and diacylglycerol (DAG)-dependent serine/threonine-protein kinase that is involved in the regulation of cell differentiation in keratinocytes, mediates regulation of epithelial tight junction integrity. Regulates epithelial tight junctions (TJs) by phosphorylating occludin (OCLN) on threonine residues, which is necessary for the assembly and maintenance of TJs.
<b>PKCm (PKD)</b>	S738+S742	-0.87	-1.96	Serine/threonine-protein kinase that converts transient diacylglycerol (DAG) signals into prolonged physiological effects downstream of PKC. Aids in regulation of JNK and Ras signaling, Golgi membrane integrity and trafficking, cell survival through NFκB activation, cell migration, cell differentiation by mediating HDAC7 nuclear export, cell proliferation via ERK1/2 signaling, and plays a role in cardiac hypertrophy, VEGFA-induced angiogenesis, genotoxic-induced apoptosis and flagellin-stimulated inflammatory response.
<b>PLCg1</b>	Y771	-0.69	-1.41	Mediates the production of the second messenger molecules diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). Plays an important role in the regulation of intracellular signaling cascades. Becomes activated in response to ligand-mediated activation of receptor-type tyrosine kinases, such as PDGFRA, PDGFRB, FGFR1, FGFR2, FGFR3 and FGFR4. Plays a role in actin reorganization and cell migration.
	Y783	-0.82	-1.76	
<b>PP2A/Ca</b>	Pan-specific	-0.54	-1.19	PP2A is the major phosphatase for microtubule-associated proteins (MAPs). Modulates the activity of phosphorylase B kinase casein kinase 2, mitogen-stimulated S6 kinase, and MAP-2 kinase. Can dephosphorylate SV40 large T antigen and p53/TP53. Activates RAF1 by dephosphorylating it at 'Ser-259'.
<b>PRK2 (PKN2)</b>	Pan-specific	0.90	1.04	PKC-related serine/threonine-protein kinase and Rho/Rac effector protein: regulates cell cycle progression, actin cytoskeleton assembly, cell migration, cell adhesion, tumor cell invasion and transcription activation signaling processes. Phosphorylates CTTN and HDAC5. Direct RhoA target required for the regulation of the maturation of primordial junctions into apical junction formation in bronchial epithelial cells. Required for G2/M phases of the cell cycle progression and abscission during cytokinesis. Stimulates FYN kinase activity that is required for skin cell-cell adhesion during keratinocyte differentiation.
<b>ROKα (ROCK2)</b>	Pan-specific	0.81	0.97	Protein kinase that regulates the actin cytoskeleton, cell polarity, smooth muscle contraction, stress fiber and focal adhesion formation, neurite retraction, cell adhesion and motility. Phosphorylates ADD1, BRCA2, CNN1, EZR, DPYSL2, EP300, MSN, MYL9/MLC2, NPM1, RDX, PPP1R12A, VIM, SORL1 and IRF4. Acts as a negative regulator of VEGF-induced angiogenic endothelial cell activation. Positively regulates the activation of p42/MAPK1-p44/MAPK3 and of p90RSK/RPS6KA1 during myogenic differentiation. Inhibits keratinocyte terminal differentiation.
<b>Src</b>	Y530	1.71	1.70	Non-receptor protein tyrosine kinase: activated following engagement of many different classes of cellular receptors (i.e. immune response receptors, integrins and other adhesion receptors, receptor protein tyrosine kinases, G protein-coupled receptors and cytokine receptors). Participates in signaling pathways that control a diverse spectrum of biological activities including gene transcription, immune response, cell adhesion, cell cycle progression, apoptosis, migration, and transformation. Also plays a role in EGF-mediated calcium-activated chloride channel activation.
	Pan-specific	1.28	1.33	
	Pan-specific	1.56	1.30	
	Pan-specific	1.36	1.24	
<b>Tau</b>	S516	0.84	0.95	Promotes microtubule assembly and stability, as well as establishment and maintenance of neuronal polarity. The short isoforms allow plasticity of the cytoskeleton whereas the longer isoforms may preferentially play a role in its stabilization.
<b>Tyro10 (DDR2)</b>	Pan-specific	-0.46	-0.99	Tyrosine kinase: functions as cell surface receptor for fibrillar collagen and regulates cell differentiation, remodeling of the extracellular matrix (via collagenases MMP1, MMP2 and MMP13), cell migration and cell proliferation. Also required for normal bone development by regulating osteoblast differentiation and chondrocyte maturation via MAPK signaling. Promotes fibroblast migration and proliferation to allow cutaneous wound healing.
<b>Vimentin</b>	S34	-1.00	-2.16	Vimentins are class-III intermediate filaments found in various non-epithelial cells, especially mesenchymal cells. Vimentin is attached to the nucleus, endoplasmic reticulum, and mitochondria, either laterally or terminally.
<b>DNA Damage Repair and Remodeling</b>				
<b>Acet. Lysine</b>	Pan-specific	1.60	1.52	DNA-remodeling (regulates histone interactions)
<b>BRCA1</b>	S1423	0.92	0.99	E3 ubiquitin-protein ligase: plays a central role in DNA repair by facilitating cellular responses to DNA damage. Required for normal cell cycle progression from G2 to mitosis as well as for appropriate cell cycle arrests after ionizing irradiation. Involved in transcriptional regulation of P21 in response to DNA damage and in targeting FANCD2 to sites of DNA damage.
<b>DNAPK</b>	Pan-specific	-0.48	-1.01	Serine/threonine-protein kinase that acts as a molecular sensor for DNA damage. Involved in DNA non-homologous end joining (NHEJ) required for double-strand break (DSB) repair and V(D)J recombination. Must be bound to DNA to express its catalytic properties. May also act as a scaffold protein to aid the localization of DNA repair proteins to the site of damage. Phosphorylates H2AX/H2AFX, DCLRE1C, c-Abl/ABL1, histone H1, HSPCA, c-jun/JUN, p53/TP53, PARP1, POU2F1, DHX9, SRF, XRCC1, XRCC1, XRCC4, XRCC5, XRCC6, WRN, MYC and RFA2.
<b>hHR23B</b>	Pan-specific	-0.64	-1.28	Involved in global genome nucleotide excision repair (GG-NER) by acting as component of the XPC complex. Cooperatively with CETN2 appears to stabilize XPC. Multiubiquitin chain receptor involved in modulation of proteasomal degradation; binds simultaneously to the 26S proteasome and polyubiquitinated substrates to deliver ubiquitinated proteins to the proteasome.
<b>MSH2</b>	Pan-specific	1.12	1.13	Component of the post-replicative DNA mismatch repair system (MMR). Forms two different heterodimers: MutS alpha (MSH2-MSH6 heterodimer) and MutS beta (MSH2-MSH3 heterodimer) which bind to DNA mismatches thereby initiating DNA repair. MutS has ATPase activity, and mismatched DNA provokes the ADP to ATP exchange to allow repair. MutS alpha may also aid DNA homologous recombination repair.
<b>PARP1</b>	Pan-specific	-0.81	-1.75	Involved in the base excision repair pathway: catalyzes the poly(ADP-ribosyl)ation of proteins involved in chromatin architecture and in DNA metabolism to signal for DNA repair. PARP1-dependent PARP9-DTX3L-mediated ubiquitination promotes the rapid and specific recruitment of 53BP1/TP53BP1, UIMC1/RAP80, and BRCA1 to DNA damage sites.
<b>SMC1</b>	S957	1.42	1.38	Involved in chromosome cohesion of sister chromatids during the cell cycle and in DNA repair via its interaction with BRCA1 and ATM.
<b>Cell Cycle Regulation</b>				
<b>CDKL1</b>	Pan-specific	-0.45	-1.30	Cyclin dependent kinase with Ser/Thr kinase activity.
<b>p107</b>	Pan-specific	-0.84	-1.57	Key regulator of transcription and entry into cell division: maintains overall chromatin structure and stabilizes histone methylation by recruiting histone methyltransferases SUV420H1 and SUV420H2. Forms a complex with adenovirus E1A and with SV40 large T antigen.
<b>p27 Kip1</b>	T187	2.40	1.04	Regulates cell cycle progression: involved in G1 arrest and inhibits cyclin E- and cyclin A-CDK2 complexes. Complexes with cyclin type D-CDK4 complexes and aids in assembly and stabilization of CCND1-CDK4 complex.

<b>Plk1</b>	Pan-specific	-0.54	-1.53	Serine/threonine-protein kinase: regulates the M phase of the cell cycle by controlling centrosome maturation and spindle assembly, the removal of cohesins from chromosome arms, the inactivation of anaphase-promoting complex/cyclosome (APC/C) inhibitors, and the regulation of mitotic exit and cytokinesis. Also negatively regulates p53 family members and is required for recovery after the DNA damage checkpoint to enter mitosis.
<b>Plk2</b>	Pan-specific	-0.39	-0.96	Tumor suppressor serine/threonine-protein kinase: involved in synaptic plasticity, centriole duplication and G1/S phase transition. Polo-like kinases bind and phosphorylate proteins that are already phosphorylated on a specific motif recognized by the POLO box domains. Phosphorylates CENPJ, NPM1, RAPGEF2, RASGRF1, SNCA, SIPA1L1 and SYNGAP1. Plays a key role in synaptic plasticity and memory by regulating the Ras and Rap protein signaling.
<b>PP1/Ca</b>	T320	-0.60	-1.57	Protein phosphatase that associates with over 200 regulatory proteins to form highly specific holoenzymes which dephosphorylate hundreds of biological targets. Essential for cell division and participates in the regulation of glycogen metabolism, muscle contractility, protein synthesis, and changes in chromatin structure. Also involved in regulation of ionic conductances and long-term synaptic plasticity.
<b>PRK2 (PKN2)</b>	Pan-specific	0.90	1.04	PKC-related serine/threonine-protein kinase and Rho/Rac effector protein: regulates cell cycle progression, actin cytoskeleton assembly, cell migration, cell adhesion, tumor cell invasion and transcription activation signaling processes. Phosphorylates CTTN and HDAC5. Direct RhoA target required for the regulation of the maturation of primordial junctions into apical junction formation in bronchial epithelial cells. Required for G2/M phases of the cell cycle progression and abscission during cytokinesis. Stimulates FYN kinase activity that is required for skin cell-cell adhesion during keratinocyte differentiation.
<b>Rb</b>	Pan-specific	2.43	2.13	Key regulator of entry into cell division and a major tumor suppressor. Promotes G0-G1 transition upon phosphorylation by CDK3/cyclin-C. The underphosphorylated, active form of RB1 interacts with E2F1 and represses its transcription activity, leading to cell cycle arrest. Directly involved in heterochromatin formation by maintaining overall chromatin structure and stabilizes histone methylation. Recruits and targets histone methyltransferases SUV39H1, SUV420H1 and SUV420H2. Inhibits TAF1 and transcription of SMARCA4/BRG1 by recruiting the HDAC complex to the c-FOS promoter. Upon calcium influx, RB1 is dephosphorylated by calcineurin, which leads to release of the repressor complex.
<b>Vrk1</b>	Pan-specific	-0.63	-1.41	Serine/threonine kinase involved in Golgi disassembly during the cell cycle: following phosphorylation by PLK3 during mitosis, required to induce Golgi fragmentation. Prevents the interaction between p53/TP53 and MDM2. Phosphorylates casein, histone H3, ATF2 and BANF1.
<b>Wee1</b>	Pan-specific	-0.92	-2.00	Acts as a negative regulator of entry into mitosis (G2 to M transition): phosphorylates and inactivates cyclin B1-complexed CDK1. Its activity increases during S and G2 phases and decreases at M phase when it is hyperphosphorylated.
<b>WIP1</b>	Pan-specific	-0.77	-1.59	Required for the relief of p53-dependent checkpoint mediated cell cycle arrest. Binds to and dephosphorylates p53 and CHEK1 to inactivate them.
<b>Translation</b>				
<b>eIF2a</b>	Pan-specific	-0.43	-1.01	Protein synthesis: forms a complex with GTP and initiator tRNA, which then binds to 40S ribosomal subunits.
	S52	-0.69	-1.35	
<b>eIF4E</b>	S209	-0.58	-1.30	Protein synthesis: recognizes and binds the 7-methylguanosine-containing mRNA cap in the initiation of protein synthesis and facilitates ribosome binding by inducing the unwinding of the mRNAs secondary structures.
<b>eIF4E</b>	Pan-specific	-0.84	-1.83	
<b>eIF4G</b>	S1107	-0.61	-1.02	Protein synthesis: component of the protein complex eIF4F, which is involved in the recognition of the mRNA cap, ATP-dependent unwinding of 5'-terminal secondary structure and recruitment of mRNA to the ribosome.
<b>PKR1</b>	Pan-specific	-0.49	-1.05	Negative regulator of translation: IFN-induced dsRNA-dependent serine/threonine-protein kinase which plays a key role in the innate immune response to viral infection and is also involved in the regulation of signal transduction, apoptosis, cell proliferation and differentiation. Inhibits viral replication via phosphorylation of the alpha subunit of EIF2S1.
	T446	-0.80	-1.73	
<b>ZPK</b>	Pan-specific	-0.61	-1.29	Inhibitor of translation: Serine/threonine kinase which is involved in the regulation of apoptosis, autophagy, transcription, translation, actin cytoskeleton reorganization, cell motility, smooth muscle contraction, and mitosis, particularly cytokinesis. Acts by phosphorylating RPL13A in response to interferon-gamma activation.
<b>Possible Roles in Other Cell and Tissue Types</b>				
<b>Brain Function</b>				
<b>CaMK1d</b>	Pan-specific	1.47	1.54	Calcium/calmodulin-dependent protein kinase that operates in the calcium-triggered CaMKK-CaMK1 signaling cascade and activates CREB-dependent gene transcription in response to calcium influx. Also promotes basal dendritic growth of hippocampal neurons and activates the transcription factor CREB1.
<b>CPG16/CaMKinase V</b>	Pan-specific	2.81	2.27	Probable kinase that may be involved in a calcium-signaling pathway controlling neuronal migration in the developing brain. May also participate in functions of the mature nervous system.
<b>GluR1</b>	S849	1.60	1.70	Ionotropic glutamate receptor. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system. Binding of the excitatory neurotransmitter L-glutamate induces a conformation change, leading to the opening of the cation channel, and thereby converts the chemical signal to an electrical impulse.
<b>GRK2 (BARK1)</b>	Pan-specific	0.84	1.09	Specifically phosphorylates the agonist-occupied form of the beta-adrenergic and closely related receptors, probably inducing their desensitization.
	S670	0.69	0.97	
<b>PP1/Ca</b>	T320	-0.60	-1.57	Protein phosphatase that associates with over 200 regulatory proteins to form highly specific holoenzymes which dephosphorylate hundreds of biological targets. Essential for cell division and participates in the regulation of glycogen metabolism, muscle contractility, protein synthesis, and changes in chromatin structure. Also involved in regulation of ionic conductances and long-term synaptic plasticity.
<b>PKCg</b>	T674	-0.90	-1.77	Calcium-activated, phospholipid- and diacylglycerol (DAG)-dependent serine/threonine-protein kinase that plays diverse roles in neuronal cells and eye tissues, such as regulation of the neuronal receptors GRIA4/GLUR4 and GRIN1/NMDAR1, modulation of receptors and neuronal functions related to sensitivity to opiates, pain and alcohol, mediation of synaptic function and cell survival after ischemia, and inhibition of gap junction activity after oxidative stress.
<b>PKG1a</b>	Pan-specific	-0.54	-1.39	Serine/threonine protein kinase: key mediator of the nitric oxide (NO)/cGMP signaling pathway and aids in the regulation of platelet activation and adhesion, smooth muscle contraction, cardiac function, gene expression, axon guidance, hippocampal and cerebellar learning, circadian rhythm and nociception. Regulates intracellular calcium levels via several pathways.
<b>PKG1</b>	Pan-specific	-0.78	-1.71	
<b>PSD-95</b>	Pan-specific	1.20	1.25	Interacts with the cytoplasmic tail of NMDA receptor subunits and shaker-type potassium channels. Required for synaptic plasticity associated with NMDA receptor signaling.
<b>SNCA</b>	S129	2.82	2.10	May be involved in the regulation of dopamine release and transport. Induces fibrillization of microtubule-associated protein tau. Reduces neuronal responsiveness to various apoptotic stimuli, leading to a decreased caspase-3 activation.
<b>Synapsin 1</b>	S9	2.92	1.85	Neuronal phosphoprotein that coats synaptic vesicles, binds to the cytoskeleton, and is believed to function in the regulation of neurotransmitter release. The complex formed with NOS1 and CAPON proteins is necessary for specific nitric-oxid functions at a presynaptic level.
<b>Tyrosine Hydroxylase</b>	S18	-0.76	-1.77	Plays an important role in the physiology of adrenergic neurons.
	S70	-1.14	-2.95	
<b>Muscle and Skeletal Tissue</b>				
<b>SOX9</b>	S181	1.62	1.86	Plays an important role in the normal skeletal development. May regulate the expression of other genes involved in chondrogenesis by acting as a transcription factor for these genes.

MLC(MLRC2)	S19	0.79	1.11	Myosin regulatory subunit that plays an important role in regulation of both smooth muscle and nonmuscle cell contractile activity via its phosphorylation. Implicated in cytokinesis, receptor capping, and cell locomotion.
<b>Endothelial Cell Signaling</b>				
PKCb1	Pan-specific	-0.91	-1.90	In endothelial cells, induces increased phosphorylation of RB1, increased VEGFA-induced cell proliferation, and inhibits PI3K/AKT-dependent nitric oxide synthase (NOS3/eNOS) regulation by insulin, which causes endothelial dysfunction. Also involved in triglyceride homeostasis. Phosphorylates the ATF2 transcription factor.
VEGF-C	Pan-specific	-0.91	-1.85	Growth factor active in angiogenesis and endothelial cell growth: stimulates proliferation and migration and regulates blood vessel permeability. Binds and activates VEGFR-2 (KDR/FLK1) and VEGFR-3 (FLT4) receptors.
VEGFR2 (KDR)	Y1059	-0.99	-2.07	Tyrosine-protein kinase: cell-surface receptor for VEGFA, VEGFC and VEGFD. Regulates angiogenesis, vascular development, vascular permeability, and embryonic hematopoiesis. Promotes proliferation, survival, migration and differentiation of endothelial cells. Promotes reorganization of the actin cytoskeleton. Activation leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate and the activation of protein kinase C. Also mediates activation of ERK1/2, AKT1, and PIK3R1 (regulatory subunit of PI3K) and promotes phosphorylation of FYN, NCK1, NOS3, PIK3R1, PTK2/FAK1 and SRC.
	Y1214	-1.10	-2.57	
<b>Leukocyte Signaling</b>				
CaMK1d	Pan-specific	1.47	1.54	Calcium/calmodulin-dependent protein kinase that operates in the calcium-triggered CaMKK-CaMK1 signaling cascade and CREB-dependent gene transcription. Regulates calcium-mediated granulocyte functions, including cytokine-induced proliferative responses and activation of the respiratory burst.
Csk	Pan-specific	3.55	2.73	Non-receptor tyrosine-protein kinase that plays an important role in the regulation of cell growth, differentiation, migration and immune response. Phosphorylates Src-family kinases (LCK, SRC, HCK, FYN, LYN and YES1). Suppresses signaling by various surface receptors, including T-cell receptor (TCR) and B-cell receptor (BCR) by phosphorylating and maintaining inactive several positive effectors such as FYN or LCK.
Fyn	Pan-specific	1.44	1.54	Non-receptor tyrosine-protein kinase that plays a role in many biological processes including regulation of cell growth and survival, cell adhesion, integrin-mediated signaling, cytoskeletal remodeling, cell motility, immune response and axon guidance. Participates in the downstream signaling pathways that lead to T-cell differentiation and proliferation following T-cell receptor (TCR) stimulation. Also participates in negative feedback regulation of TCR signaling through phosphorylation of PAG1, thereby promoting interaction between PAG1 and CSK and recruitment of CSK to lipid rafts.
JAK1	Y1034	0.98	0.95	Tyrosine kinase of the non-receptor type, involved in the IFN-alpha/beta/gamma signal pathway. Kinase partner for the interleukin (IL)-2 receptor.
Lck	Y192	-0.71	-1.21	Non-receptor tyrosine-protein kinase that plays an essential role in the selection and maturation of developing T-cells in the thymus, in the function of mature T-cells, and in T-cell proliferation. Plays a key role in T-cell antigen receptor (TCR)-linked signal transduction pathways and associates with the cytoplasmic portions of the CD4 and CD8 surface receptors. Association of the TCR with a peptide antigen-bound MHC complex facilitates the interaction of CD4 and CD8 with MHC class II and class I molecules, respectively, thereby recruiting the associated LCK protein to the vicinity of the TCR/CD3 complex. Also phosphorylates other substrates including RUNX3, PTK2B/PYK2, the microtubule-associated protein MAPT, RHOH or TYROBP.
	S158	-0.74	-1.22	
	Pan-specific	-0.68	-1.22	
	Y394	-0.73	-1.56	
	Y505	-0.80	-1.57	
Pan-specific	-0.79	-1.70		
PKCb1	Pan-specific	-0.91	-1.90	Calcium-activated, phospholipid- and diacylglycerol (DAG)-dependent serine/threonine-protein kinase involved in regulation of B-cell receptor (BCR) signaling, oxidative stress-induced apoptosis, androgen receptor-dependent transcription regulation, insulin signaling and endothelial cells proliferation.
PKCd	S645	-0.74	-1.60	Regulates TNF-elicited superoxide anion production in neutrophils through phosphorylation of NCF1 or ERK1/2 signaling pathways. Also regulates NADPH oxidase activity in eosinophils after stimulation with IL5, leukotriene B4 or PMA and acts a negative regulator of filopodia formation and actin polymerization. Regulates the interaction between MUC1 and beta-catenin by phosphorylating MUC1. Also phosphorylates 14-3-3 proteins (YWHAB, YWHAZ and YWHAH) in a sphingosine-dependent fashion.
PKCq	S695	-0.78	-1.69	Calcium-independent, phospholipid- and diacylglycerol (DAG)-dependent serine/threonine-protein kinase that mediates non-redundant functions in T-cell receptor (TCR) signaling, including T-cell activation, proliferation, differentiation and survival, by mediating activation of NFkB, JUN, NFATC1 and NFATC2. Essential for IL2 production and participates in NFATC1 and NFATC2 transactivation. Aids in the regulation of inositol 1,4,5-trisphosphate generation and intracellular calcium mobilization. Promotes the development of T-helper 2 (Th2) cells and is necessary for the activation of IL17-producing Th17 cells. Mediates T-cell survival by phosphorylating BAD and by up-regulating BCL-X(L)/BCL2L1 levels. In platelets, regulates signal transduction downstream of ITGA2B, CD36/GP4, F2R/PAR1 and F2RL3/PAR4. Also phosphorylates PDPK1 to inhibit AKT1.
PKCz/l	T410/T412	-1.20	-3.27	Calcium- and diacylglycerol-independent serine/threonine-protein kinase that functions in PI3K, MAPK, and NFkB signaling cascades. Also regulates mitogenic signaling, cell proliferation, cell polarity, the inflammatory response and maintenance of long-term potentiation (LTP). Required for T-helper 2 (Th2) differentiation and efficient activation of JAK1 and STAT6.
Striatin	Pan-specific	1.14	1.37	Calmodulin-binding protein which functions as scaffolding or signaling protein and plays a role in dendritic Ca2+ signaling.
ZAP70	Pan-specific	-1.23	-2.98	Tyrosine kinase that regulates the adaptive immune response, motility, adhesion and cytokine expression of mature T-cells, as well as thymocyte and B-lymphocyte development. Induces recruitment of ZAP70 to the phosphorylated TCR components CD247/CD3Z through ITAM motifs at the plasma membrane. Promotes lymphokine production, T-cell proliferation and differentiation. During thymocyte development, ZAP70 promotes survival and cell-cycle progression of developing thymocytes before positive selection. Contributes to primary B-cell formation and activation through BCR.
ZAP70/Syk	Y319/Y352	-0.77	-2.07	