Table S1. Reactions and parameters in simple models

No.	Mathematical representation	Reaction	Parameters	Unit	Reference	Description
v1	kf1*x1*x9	ErbB3 + ErbB2 -> ErbB3_ErbB2	1.81E-04	/molecules/min	estimated	HRG binding to ErbB3 monomer
v2	kr1*x2	ErbB3_ErbB2 -> ErbB3 + ErbB2	20	/min	estimated	
v3	kf2*hrg*x1	ErbB3(+[HRG]) -> HRG:ErbB3	0.125	/uM/min	estimated	HRG binding to ErbB3 monomer
v4	kr2*x3	HRG:ErbB3 -> ErbB3(+[HRG])	20	/min	estimated	Dissociation of HRG from ErbB3 monomer
v5	kf22*hrg*x2	ErbB3_ErbB2(+[HRG])-> HRG:ErbB3_ErbB2	6	/uM/min	estimated	HRG binding to ErbB3_ErbB2 dimer
v6	kr2*x4	HRG:ErbB3_ErbB2 -> ErbB3_ErbB2(+[HRG])	20	/min	estimated	Dissociation of HRG from ErbB3_ErbB2 dimer
v7	kf3*x3*x9	HRG:ErbB3 + ErbB2 -> HRG:ErbB3_ErbB2	8.68E-03	/molecules/min	estimated	Dimer formation of HRG-bound ErbB3 and ErbB2
v8	kr3*x4	HRG:ErbB3_ErbB2 -> HRG:ErbB3 + ErbB2	20	/min	estimated	Dissociation of ErbB2 from ErbB3_ErbB2 dimer
v9	V4*x4/(Km4+x4)	HRG:ErbB3_ErbB2 -> pErbB3_pErbB2	V4 = 2000 Km4 = 2000	/min molecules	estimated	Autophosphorylation of HRG-binding ErbB3_ErbB2 dimer
v10	k5*x5*x8/(Km5+x5)	pErbB3_pErbB2 -> HRG:ErbB3_ErbB2	k5 = 1.6 Km5 = 4000	/min molecules	estimated	Dephosphorylation of pErbB3_pErbB2 mediated by PTPN
v11	kf6*x5*x5	pErbB3_pErbB2 *2 -> (pErbB3_pErbB2)2	0.002	/molecules/min	estimated	Tetramer formation of pErbB3_pErbB3 dimers
v12	kr6*x6	(pErbB3_pErbB2)2 -> pErbB3_pErbB2 *2	4	/min	estimated	Dissociation of tetramer
v13	ks7	-> PHLDA1 synthesis	[initial x7]*kd7 †	molecules/min	estimated	Basal synthesis of PHLDA1
v14	ks7d*x5+ks7dd*x6	pErbB3_pErbB2 & (pErbB3_pErbB2)2 -> PHLDA1 syr	ks7d = 0.04 ks7dd = 0.04	/min /min	estimated	Synthesis of PHLDA1 promoted by pAkt and c-Fos
v15	kd7*x7	PHLDA1 -> degradation	0.02	/min	estimated	Degradation of PHLDA1
v16	ks8*x5+ks8d*x6	pErbB3_pErbB2 & (pErbB3_pErbB2)2 -> PTPN synth	ks8 = 0.04 ks8d = 0.4	/min /min	estimated	Synthesis of PTPN promoted by pErbB3_pErbB2 dimer and tetramer
v17	kd8*x8	PTPN -> degradation	0.02	/min	estimated	Degradation of PTPN
Feedback	1 - x7/(ki+x7)	Negative feedback from PHLDA1	6000	molecules	estimated	

+ Synthetic constants of DUSP and PHLDA1 were calcurated from randomly selected initial values in the simulation with cell-to-cell variability.

Table S2. Initial concentration of molecules in simple models

Symbol	Species	Molecules/cell	Reference
HRG	Concentration of HRG	10 (uM)	Experimental condition in this study
y1	HRGR	10000	estimated based on [1]
y2	HRGR_ErbB2	0	
уЗ	HRG:HRGR	0	
y4	HRG:HRGR_ErbB2	0	
у5	pHRGR_pErbB2	0	
у6	(pHRGR_pErbB2)2	0	
у7	PHLDA1	6000	estimated
y8	Phosphatase	0	
у9	ErbB2	8000	estimated based on [1]

[1] Zhang, Q., Park, E., Kani, K., and Landgraf, R. (2012). Proc. Natl. Acad. Sci. USA 109, 13237–13242

Table S3. CV of molecules in simple models

Species	CV of protein concentrations (%)	Reference
HRGR	31	estimated by measuring CV of ErbB3 (Fig. 3D)
ErbB2	40	macaured in this study (Fig. 2D)
PHLDA1	100	measured in this study (Fig. 3D)

Table S4. Rank correlations in simple models

Species	Rank correlation	Reference
		estimated by measuring rank
HRGR-PHLDA1	0.13	correlation between ErbB3 & PHLDA1
		(Fig. 3F)
	0.05	measured in this study
EIUDZ-PHLDAI	0.25	(Fig. 3F)

Table S5	. Negative	feedback	from	PHLDA1	in sir	nple	models

Name	Reactions inhibited by negative feedback from PHLDA1	Description
Model M0	-	No feedback from PHLDA1
Model M1	v1 and v7	Inhibition of dimer formation
Model M2	v9	Inhibition of phosphorylation
Model M3	v11	Inhibition of tetramer formation
Model M4	v1, v7 and v11	Inhibition of dimer and tetramer formation

Table S6. Reactions and parameters in the expanded model

	Heaction	mathematical representation	Parameters	vaiue	Unit	reterence	Description
omp	lex formation of ErbB receptors		1.5.0	2 34 5 04	(male)	fitted	
/1	HRGR + ErbB2 -> HRGR ErbB2	kb0 1*v1*v59 + kb0 2*v1*v59*ki/(ki+v57)	kb0_1 kb0_2	2.34.E-04 2.71.E-05	/molecules/s /molecules/s	fitted	Dimer formation of HRGR and ErbB2 inhibited by PHLDA1 (this study)
		,.,.,,,,,,,,,,,,,,,,,,,,,,,,,,,	ki	4.19.E+07	molecules	fitted	
2	HRGR_ErbB2 -> HRGR + ErbB2	kd0*y2	kd0	8.16.E-01	/s	fitted	Dissociation of ErbB2 from HRGR_ErbB2 dimer
14 14	HRG:HRGR -> HRGR(+[HRG])	kd1*y3	kd1	1.10.E+04	/u////////////////////////////////////	fitted	Dissociation of HRG from HRGR monomer
5	HRGR_ErbB2(+[HRG])-> HRG:HRGR_ErbB2	kb1*y2*HRG	kb1	3.37.E+01	/uM/s	fitted	HRG binding to HRGR_ErbB2 dimer
6	HRG:HRGR_ErbB2 -> HRGR_ErbB2(+[HRG])	kd1*y4	kd1	1.10.E+04	/s	fitted	Dissociation of HRG from HRGR_ErbB2 dimer
7		kdim1*v3 + kdim2*v2*bi//bi-v57	kdim2	4.18.E-02	/molecules/s	fitted	Dimer formation of HBG-bound HBGB and ErbB2 inhibited by PHLDA1 (this study)
		Kullini yo + Kullinz yo Ki/(ki+yo/)	ki	4.19.E+07	molecules	fitted	bine formation of the board threat and Elobe inhibited by the bert (this study)
/8	HRG:HRGR_ErbB2 -> HRG:HRGR + ErbB2	kmono*y4	kmono	8.60.E+00	/s	fitted	Dissociation of ErbB2 from HRG-binding HRGR_ErbB2 dimer
/9	HRG:HRGR_ErbB2 -> pHRGR_pErbB2	k1*y4*y4	k1	1.00.E-02	/molecules/s	fitted	Autophosphorylation of HRG-binding HRGR_ErbB2 dimer
10	pHRGR_pErbB2 -> HRG:HRGR_ErbB2	k2*y58*y5/(km2+y5)	k2	7.35.E+02	/s	fitted	Dephosphorylation of pHRGR_pErbB2 mediated by PTPN
			ktet1	2.26.E+05 2.76 E±02	molecules	fitted	
/11	pHRGR pErbB2 *2 -> (pHRGR pErbB2)2	ktet1*v5*v5 + ktet2*v5*v5*ki/(ki+v57)	ktet2	3.20.E+01	/molecules/s	fitted	Tetramer formation of pHRGR pHRGR dimers inhibited by PHLDA1 (this study)
	P		ki	4.19.E+07	molecules	fitted	······································
12	(pHRGR_pErbB2)2 -> pHRGR_pErbB2 *2	kdim*y3d	kdim	8.98.E+01	/s	fitted	Dissociation of tetramer
13K-/	Akt pathway						
3	pHRGR_pErbB2+PI3K ->	kf3*y5*y7	kf3	1.08E-01	/molecules/s	fitted	Phosphorylation of PI3K by pHRGR_pErbB2 dimer
14	pHRGR_pErbB2_PI3K -> pHRGR_pErbB2+PI3K	kr3*y8	kr3	1.62E+02	/s	fitted	
15	pHRGR_pErbB2_PI3K -> pHRGR_pErbB2+PI3KA	KC3*y8 kf3*v6*v7	KC3 kf2	4.74E+00 1.08E-01	/S /moleculee/c	fitted	Phoenborulation of PI3K by pHDCP pErbP3 totramor
10 17	$(pHRGR pErbB2)2+PI3K \rightarrow (pHRGR pErbB2)2+PI3K$	kr3*v9	kr3	1.62E+02	/molecules/s /s	fitted	Filosphorylation of Plan by princin_perob2 tetramer
18	(pHRGR_pErbB2)2_PI3K -> (pHRGR_pErbB2)2+PI3KA	kc3d*y9	kc3d	4.40E+00	/s	fitted	
19	PIP2 + PI3KA ->	kf4*y10*y11	kf4	1.28E-03	/molecules/s	fitted	Phosphorylation of PIP2 by PI3K
20	PI3KA_PIP2 -> PIP2 + PI3KA	kr4*y12	kr4	1.38E+02	/s	fitted	
21	PI3KA_PIP2 -> PIP3 + PI3KA	kf5*v13*v14	kC4 kf5	1.90E+01 1.68E-04	/S /molecules/e	fitted	Phoenbory/ation of PDK1
 23	PIP3 PDK1 -> PIP3 + PDK1	kr5*y15	kr5	3.08E+02	/s	fitted	i nosphoryiallUli Ul FDK i
24	PIP3_PDK1 -> PIP3 + p-PDK1	kc5*y15	kc5	3.45E+02	/s	fitted	
25	p-PDK1 + Akt ->	kf6*y16*y17	kf6	5.02E-03	/molecules/s	fitted	Phosphorylation of Akt by PDK1
26	p-PDK1_Akt -> p-PDK1 + Akt	kr6*y18	kr6	3.81E+02	/s	fitted	
27 28	p-PUK1_AKt -> p-PUK1 + p-AKt PI3KA + Pase1 ->	kf7*v10*v20	ксо kf7	7.16F-04	/s /molecules/s	fitted	Dephosphorylation of PI3K
29	Pase1_PI3KA -> PI3KA + Pase1	kr7*y21	kr7	3.64E+00	/s	fitted	
30	Pase1_PI3KA -> PI3K + Pase1	kc7*y21	kc7	4.34E+00	/s	fitted	
31	PIP3 + PTEN ->	kf8*y13*y22	kf8	6.56E-03	/molecules/s	fitted	Dephosphorylation of PIP3 by PTEN
32	PTEN_PIP3 -> PIP3 + PTEN DTEN_DIP3 -> DIP3 + DTEN	KT8 1/23 kc8*//23	Kr8 kc ⁹	1.21E+02 1.11E+02	/S /e	fitted	
53 34	n-PDK1 + Pase2 ->	kf9*y16*y24	kf9	4.30E-03	/molecules/s	fitted	Dephosphorylation of PDK
35	Pase2_p-PDK1 -> p-PDK1 + Pase2	kr9*y25	kr9	1.53E+01	/s	fitted	
/36	Pase2_p-PDK1 -> PDK1 + Pase2	kc9*y25	kc9	1.68E+02	/s	fitted	
37	p-Akt + PP2A ->	kr10'y19'y26	kt10	1.12E-03	/molecules/s	fitted	Dephosphorylation of pAkt by PP2A
აფ 39	$PP2A p-Akt \rightarrow PAkt + PP2A$	kc10*y27	kc10	5.22E+02	/s /s	fitted	
		,			-		
as-E	RK pathway	kf11*v5*v28	kf11	2 41E-01	/molecules/c	6m1	Astivition of ReaCOR by pHRCR a ErbRd dimen
/4U /41	pEludz_pHHGH+HasGUP -> pHBGB_pErbB2_BasGDP> p-ErbB + BasGDP	kr11*y29	kr11	2.32E+03	/s	fitted	Activation of Hascoph by princin_perode2 dimer
42	pHRGR_pErbB2_RasGDP -> p-ErbB + RasGTP	kc11*y29	kc11	5.54E+02	/s	fitted	
43	(pErbB2_pHRGR)2+RasGDP ->	kf11*y6*y28	kf11	2.41E-01	/molecules/s	fitted	Activation of RasGDP by pHRGR_pErbB2 tetramer
44	(pHRGR_pErbB2)2_RasGDP -> (pErbB2_pHRGR)2+RasGDP	kr11*y30	kr11	2.32E+03	/s	fitted	
45	(pringh_perob2)2_HasGDP -> (pErbB2_pHRGR)2+RasGTP BasGTP -> BasGDP	k12*v31	кс (10 k12	1.39E+04 3.76E±03	/S /e	fitted	Inactivation of BasGTP
47	RasGTP + Raf ->	kf13*y31*y32	kf13	3.32E-02	/molecules/s	fitted	Activation of Raf by RasGTP
48	RasGTP_Raf -> RasGTP + Raf	kr13*y33	kr13	8.04E+01	/s	fitted	·····
49	RasGTP_Raf -> RasGDP + p-Raf	kc13*y33	kc13	6.17E+02	/s	fitted	
50	p-Rat + MEK ->	ki 14 y34 y35 kr14*v36	kr14 kr14	5.30E-03 1.46F±03	/molecules/s	fitted	Phosphorylation of MEK by Raf
J1 /52	p-nat - MEK -> p-Raf + MEK	kc14*y36	kc14	5.79E+04	/s	fitted	
53	p-Raf + p-MEK ->	kf15*y34*y37	kf15	1.32E-01	/molecules/s	fitted	Phosphorylation of p-MEK by Raf
54	p-Raf_p-MEK -> p-Raf + p-MEK	kr15*y38	kr15	4.45E+03	/s	fitted	
55	p-Raf_p-MEK -> p-Raf + pp-MEK	kc15*y38	kc15	7.00E+03	/s /moloc::/	fitted	Description of EDV by MEV
dc	pp-MEK + ERK ->	kr16*v41	kr16	1.81E-03 8.46F±02	/molecules/s	fitted	Phosphorylation of EHK by MEK
57	pp-MEK ERK -> pp-MEK + p-ERK	kc16*v41	kc16	1.80E+02	/s	fitted	
57 58					-		
57 58 59	pp-MEK + p-ERK ->	kf17*y39*y42	kf17	1.78E-02	/molecules/s	fitted	Phosphorylation of p-EHK by MEK
57 58 59 60	pp-MEK + p-ERK -> pp-MEK_p-ERK -> pp-MEK + p-ERK	kf17*y39*y42 kr17*y43	kf17 kr17	1.78E-02 1.50E+01	/molecules/s /s	fitted	Phosphorylation of p-EHK by MEK
57 58 59 60 61	pp-MEK + p-ERK -> pp-MEK_p-ERK -> pp-MEK + p-ERK pp-MEK_p-ERK -> pp-MEK + pp-ERK	k117'y39'y42 kr17'y43 kc17'y43 k19'y44y45	kf17 kr17 kc17	1.78E-02 1.50E+01 1.01E+02 5.20E-05	/molecules/s /s /s	fitted fitted fitted	Phosphorylation of p-EHK by MEK
57 58 59 60 61 62 63	pp-MEK + p-ERK -> pp-MEK_p-ERK -> pp-MEK + p-ERK pp-MEK_p-ERK -> pp-MEK + pp-ERK RSK + pp-ERK -> PSK	kf17*ý39*y42 kr17*y43 kr17*y43 kf18*y44*y45 kr18*y44*y45	kf17 kr17 kc17 kf18 kr18	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02	/molecules/s /s /molecules/s /s	fitted fitted fitted fitted fitted	Phosphorylation of P-EHK by MEK Phosphorylation of RSK by ERK
57 58 59 60 61 62 63 64	pp-MEK + p-ERK >> pp-MEK _ p-ERK >>pp-MEK + p-ERK pp-MEK _ p-FRK >> pp-MEK + pp-ERK RSK + pp-ERK >> RSK _ pp-ERK >> RSK _ pp-ERK >> RSK _ pp-ERK >>	k17*ý39*y42 kr17*y43 kc17*y43 k18*y44*y45 kr18*y46 kc18*y46 kc18*y46	kf17 kr17 kc17 kf18 kr18 kc18	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00	/molecules/s /s /molecules/s /s /s	fitted fitted fitted fitted fitted fitted	Phosphorylation of P.EHK by MEK
57 58 59 60 61 62 63 64 65	pp-MEK ↓ p-ERK → pp-MEK + p-ERK pp-MEK _p-ERK → pp-MEK + p-ERK RSK + pp-ERK → pp-MEK + pp-ERK RSK _pp-ERK → RSK + pp-ERK RSK _pp-ERK → RSK + pp-ERK p-RSK → RSK → S-RSK	k17*y39*y42 kr17*y43 kc17*y43 k118*y44*y45 kc18*y46 kc18*y46 kc18*y46 k19*y47	kf17 kr17 kc17 kf18 kr18 kc18 kc18	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01	/molecules/s /s /molecules/s /s /s /s	fitted fitted fitted fitted fitted fitted fitted	Phosphorylation of P.EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of RSK
57 58 59 60 61 62 63 64 65 66	pp-MEK ↓ p=ERK > pp-MEK + p=ERK pp-MEK _ p=FRK > pp-MEK + pp-ERK RSK + pp-ERK > RSK _ pp=ERK > RSK _ pp=ERK > RSK + pp=ERK RSK _ p=RK > RSK + pp=ERK p=RSK > RSK = pp=RK	k17'y30'y42 kr17'y43 kr17'y43 kr18'y44'y45 kr18'y46 kr18'y46 kr19'y46 k19'y47 k120'y34'y48	kf17 kr17 kc17 kf18 kr18 kc18 k19 kf20	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 2.15E-01 4.17E - 22	/molecules/s /s /molecules/s /s /s /molecules/s /molecules/s	fitted fitted fitted fitted fitted fitted fitted	Phosphorylation of p-EHK by MEK Dephosphorylation of PSK Deadtivation of p-Raf
57 58 59 60 61 62 63 64 65 66 65 66	pp-MEK + p-ERK → pp-MEK + p-ERK pp-MEK _ pERK → pp-MEK + p-ERK RSK + pp-ERK → pm-MEK + pp-ERK RSK _ pp-ERK → RSK + pp-ERK RSK _ pp-ERK → PRK + pp-ERK p-RSK → PRSK → PRSK PRaid + Pasa3 → PRaid + Pasa3 Pasa3 _ p-Raid → PR in Pasa3	1177/387y42 k177y43 k177y43 1187y447y45 k187y46 k187y46 k187y46 k187y46 k187y46 k187y47 k187y46 k187y46 k207y47y48 k207y40 k207y40	kf17 kr17 kc17 kf18 kr18 kc18 k19 kf20 kr20 kr20	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 2.15E-01 1.47E+02 9.99E-01	/molecules/s /s /molecules/s /s /s /molecules/s /s /s	fitted fitted fitted fitted fitted fitted fitted fitted fitted	Phosphorylation of P.EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of RSK Deactivation of p-Raf
57 58 59 60 61 62 63 64 65 66 67 68 69	pp-MEK ↓ p-ERK → pp-MEK + p-ERK pp-MEK _ p-ERK → pp-MEK + p-ERK RSK _ pp-ERK → pp-MEK + pp-ERK RSK _ pp-ERK → RSK + pp-ERK RSK _ pp-ERK → RSK + pp-ERK p-RsK → RSK → p-RSK → p-RSK p-Rsf + Pase3 p-Rsf → p-Raf + Pase3 Pase3_p-Raf → p-Raf + Pase3 Pase3 → Raf + Pase3 Pase3 →	H177/38'Y42 H177/43 K177/43 K118'Y44'Y45 K118'Y46 K18'Y46 K19'Y47 H20'Y49 K20'Y49 K20'Y49 K20'Y49 K20'Y49	kf17 kr17 kf18 kr18 kr18 kr18 kf20 kf20 kr20 kr20 kr20 kr21	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 2.15E-01 1.47E+02 9.98E+01 3.70E-06	/molecules/s /s /molecules/s /s /s /molecules/s /s /molecules/s	fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted	Phosphorylation of P-EHK by MEK Phosphorylation of RSK Depchosphorylation of RSK Deactivation of p-Raf Dechosphorylation of cp-MEK
/57 /58 /59 /60 /61 /62 /63 /64 /65 /66 /67 /68 /69 /70	pp-MEK + p-ERK → pp-MEK + p-ERK pp-MEK _ p-ERK → pp-MEK + pp-ERK RSK + pp-ERK → RSK _ pp-ERK → RSK _ pp-ERK → RSK + pp-ERK P-RSK → RSK + pp-ERK p-RSK → RSK + pp-ERK p-RSK → RSK + pp-RK P-RSK → P-RSK → p-RSK P-RSK → P-RSK P-RSK → P-RSK → p-RSK P-RSK → P-RSK → P-RSK P-RSK + Pase3 P-RSK + Pase4 P-RSK + PASE4 P-RSK + PASE4 P-RSK + P-RSK → P-RSK P-RSK + P-RSK P-RSK + P-RSK P-RSK + P-RSK P-RSK + P-RSK + P-RSK + P-RSK P-RSK + P-RSK + P-RSK + P-RSK + P-RSK P-RSK + P-RSK	H177/39/Y42 H177/43 H187/44/Y45 K187/44/Y45 K187/46 K187/46 K187/46 H207/34/Y48 H207/34/Y48 H207/49 K207/49 K217/51	kf17 kr17 kc17 kf18 kr18 kr19 kf20 kr20 kr20 kr21 kr21	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.47E+02 9.98E+01 3.70E-06 2.42E+03	/molecules/s /s /molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s	fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted	Phosphorylation of PSK by ERK Dephosphorylation of RSK Deactivation of p-Raf Dephosphorylation of pp-MEK
/57 /58 /59 /60 /61 /62 /63 /64 /65 /66 /67 /68 /69 /70 /71	pp-MEK ↓ PERK → pp-MEK + p-ERK pp-MEK ↓ PERK → pp-MEK + p-ERK RSK ↓ pp-ERK → RSK + pp-ERK RSK µ p-ERK → RSK + pp-ERK PRSK → PRSK → PRSK → PRSK PRSK → RSK → p-RSK → PRSK PRSK → RSK → PRSK PRSK → RSK → PRSK PRSK → PRSK → PRSK Pase4 µ PMEK → PMEK + Pase4 Pase4 µ PMEK → PMEK + Pase4	H177/93'y42 H177/43 H177/43 H187/47/45 H187/47/46 K187/46 K187/47 N207/44 M207/44 K207/49 K207/49 K207/49 K207/49 K207/49 K217/35 K217/51	kf17 kr17 kr18 kr18 kr18 kr20 kr20 kr20 kr20 kr21 kr21 kr21 kr21	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 2.15E-01 1.47E+02 9.98E+01 3.70E-06 2.42E+03 2.42E+02	/molecules/s /s /molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /s	fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK Dephosphorylation of RSK Deactivation of p-Raf Dephosphorylation of pp-MEK
57 58 59 60 61 62 63 64 65 66 66 66 67 68 69 70 71 72	pp-MEK + p-ERK → pp-MEK + p-ERK pp-MEK _ p-ERK → pp-MEK + pp-ERK RSK + pp-ERK → RSK _ pp-ERK → RSK _ pp-ERK → RSK + pp-ERK p-RSK → RSK + pp-ERK p-RSK → RSK + pp-ERK p-RSK → RSK + pp-ERK p-RSK → RSK + pp-ERK Pass3 _ p-Rat + Pass3 pp-MEK + Pass4 Pass4 _ pp-MEK → pp-MEK + Pass4 Pass4 _ pp-MEK + Pass4	H17/38/y42 H17/43 K17/43 K18/44/y45 K18/46 K18/46 K18/46 K18/46 K120/34/y48 K20/49 K20/49 K20/49 K21/51 K21/51 K21/51 K21/51	kf17 kr17 kf18 kr18 kr18 kr19 kf20 kr20 kr20 kr21 kr21 kr21 kr21 kr22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 2.15E-01 1.47E+02 9.98E+01 3.70E-06 2.42E+02 6.89E-04 0.06E-02	/molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s	fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted fitted	Phosphorylation of p-EHK by MEK Phosphorylation of PSK by ERK Dephosphorylation of p-Raf Dephosphorylation of p-MEK Dephosphorylation of p-MEK
57 58 59 60 61 62 63 64 66 66 66 66 70 77 72 73 74	pp-MEK + p-ERK >> pp-MEK + pERK >> pp-MEK + pERK >> pp-MEK + pERK >> ps-MEK + pERK > ps-MEK + pERK > ps-MEK + pERK > pressort > pressort > pressort > p-Rait + Pase3 > pase3 p-Pat > pp-MEK + Pase4 > pmaxel pp-MEK > pmaxel pp-MEK + Pase4 > pmaxel pp-MEK <> > pmaxel pp-MEK <> > pmaxel pp-MEK <> > pmaxel pp-MEK <>/td> >	1117/38/y42 117/94 117/94 118/94/y45 118/94/y46 118/94 120/94/y46 120/94/y46 120/94/y46 120/94/y46 120/94/y46 120/94/y46 121/951 122/957/960 122/952	kf17 kr17 kr18 kr18 kr18 kr19 kf20 kr20 kf21 kr21 kr21 kr21 kr22 kr22 kr22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 2.15E-01 1.47E+02 9.98E+01 3.70E-06 2.42E+03 2.42E+03 2.42E+03 2.42E+04 2.96E+02 5.98E-00	/molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s	fitted fitted	Phosphorylation of PSK by ERK Dephosphorylation of RSK by ERK Dephosphorylation of P.Raf Dephosphorylation of pp-MEK Dephosphorylation of p-MEK
757 758 759 760 761 762 763 764 766 766 768 766 768 769 770 771 772 773 774 775	pp-MEK → p-ERK >> pp-MEK → p-ERK >> pp-MEK → p-ERK >> RSK → pp-ERK >> P-Rai + Pass0 >> Pass0 → Past >>	H177/38'y42 H177/43 Kc177/43 Kc177/43 Kc187/44 Kc187/46 Kc187/46 Kc187/46 Kc187/46 Kc207/49 Kc20	kf17 kc17 kf18 kc18 kc18 kf19 kf20 kc20 kf21 kc21 kc21 kc21 kc21 kc22 kc22 kc22 kc	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 2.15E-01 1.47E+02 9.98E+01 1.47E+02 9.98E+01 3.70E-06 2.42E+02 6.89E-04 2.96E+02 5.98E+00 2.43E+04	/molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s	fitted fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of RSK Deptosphorylation of pp-MEK Dephosphorylation of pp-MEK Dephosphorylation of pc-ERK by DUSP
757 758 759 760 761 762 763 764 766 768 768 769 770 771 772 773 774 775 776	pp-MEK + p-ERK >> pp-MEK + pERK >> pp-MEK + pERK >> pp-MEK + pERK >> psK + pp-ERK >> RSK + pp-ERK >> RSK + pp-ERK >> PRIS + pp-ERK > PRIS + Pase4 > Pase4 _p-MEK > PUSP_pp	H177/39'y42 H177/43 H179/44 H187/44/y45 K187/46 K187/46 K187/46 H207/34/y48 H207/44 H207/34/y48 H207/49 H217/51 K217/51 K217/51 K217/51 K2217/51 K2217/51 K2217/51 K2217/51 K2217/51 K2217/52 H227/34/y53	k117 kc17 k118 kc18 kc18 kc18 kc20 kc20 kc20 kc21 kc21 kc21 kc21 kc22 kc22 kc22 kc22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 2.15E-01 1.47E+02 9.98E+01 3.70E-06 2.42E+03 2.42E+03 2.42E+04 2.96E+00 2.98E+00 2.43E-04 3.94E+01	/molecules/s /s /s /molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s	fitted fitted	Phosphorylation of PSK by ERK Dephosphorylation of RSK by ERK Dephosphorylation of PSK Dephosphorylation of pp-MEK Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP
57 58 59 60 61 62 63 64 65 66 66 66 67 68 69 70 71 72 73 74 77 74 77 77	p→MEK + p=ERK >> p→MEK + pERK >> p→MEK + pERK >> pARS + pERK >> RSK + ppERK >> RSK + ppERK >> PASK - pERK >> PASK - pPERK >> PASK - pAR - NASK >> PASK - pAR - NASK > PASK - pPERK > PASK - PASK > <td>H177/93'Y42 H177/93 H177/94 H187/94/Y45 H187/94 K187/94 H187/94 H187/94 H207/94/Y48 H207/94/Y48 H207/94/Y48 H207/94/Y48 H217/93'Y50 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95</td> <td>k117 kc17 kc18 kc18 kc18 kc18 kc19 kc20 kc20 kc20 kc21 kc21 kc21 kc22 kc22 kc22 kc23 kc23</td> <td>1.78E-02 1.50E+01 1.51E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.75E-01 1.47E+02 9.98E+01 3.70E-06 2.42E+03 2.42E+03 2.42E+03 2.42E+04 6.89E-04 2.86E+04 3.48E+</td> <td>/molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s</td> <td>fitted fitted</td> <td>Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of p-Raf Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP</td>	H177/93'Y42 H177/93 H177/94 H187/94/Y45 H187/94 K187/94 H187/94 H187/94 H207/94/Y48 H207/94/Y48 H207/94/Y48 H207/94/Y48 H217/93'Y50 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95 H227/95	k117 kc17 kc18 kc18 kc18 kc18 kc19 kc20 kc20 kc20 kc21 kc21 kc21 kc22 kc22 kc22 kc23 kc23	1.78E-02 1.50E+01 1.51E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.75E-01 1.47E+02 9.98E+01 3.70E-06 2.42E+03 2.42E+03 2.42E+03 2.42E+04 6.89E-04 2.86E+04 3.48E+	/molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s	fitted fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of p-Raf Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP
57 58 59 60 162 63 64 56 66 70 77 77 77 77 77 77 77 77 77 77 77 77	pp-MEK + p-ERK >> pp-MEK + pERK >> pp-MEK + pERK >> pp-MEK + pERK >> RSK + pp-ERK >> RSK + pp-ERK > RSK + pp-ERK > PR0 + pp-ERK > PR1 + Pass > Pass0 -p-Rat > Pass3 -p-Rat > Pass4 -pp-MEK + Pass4	H177/38'y42 H177/43 H179/44 K177/45 K187/44 K187/46 K187/46 K187/46 K1207/347/48 K207/49 K207/49 K207/49 K217/51 K217/51 K217/51 K217/51 K2217/51 K2217/52 K227/52 K227/44 K237/44 K237/44	k117 kc17 kc18 kc18 kc18 kc18 k120 kc20 kd21 kc21 kc21 kc21 kc22 kc22 kc22 kc22 kc	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.47E+02 9.98E+01 3.70E-06 9.98E+01 3.70E-06 2.42E+02 2.68E-04 2.68E-04 2.58E+04 3.58E+04 3.54E+04 3.51E+05 5.51E+	/molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s	titled fitted	Phosphorylation of p-EHK by MEK Phosphorylation of PSK by ERK Dephosphorylation of P-Raf Dephosphorylation of p-MEK Dephosphorylation of p-MEK Dephosphorylation of p-ERK by DUSP Dephosphorylation of p-ERK by DUSP
57 58 59 60 61 62 63 64 65 66 66 66 66 70 77 77 77 77 77 77 77 77 77 79 90	pp-MEK + p-ERK >> pp-MEK + pERK >> pp-MEK + pERK >> pp-MEK + pERK >> ps-MEK + pERK >> ps-MEK + pERK > pressort >> pressort >> <td>1117/38/y42 1177/43 1187/447y45 1187/447y45 1187/447y45 1187/47 1207/47y48 1207/47y48 1207/47y48 1207/49 1207/49 1217/51 1227/37y50 1227/52 1227/52 1227/52 1227/54 1227/55 1237/55</td> <td>k117 kc17 kc18 kc18 kc18 kc18 k120 kc20 kc20 kc21 kc21 kc21 kc21 kc22 kc22 kc22 kc22</td> <td>1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.75E-01 1.47E+02 9.98E+01 3.70E-06 2.42E+02 6.89E-04 2.98E+00 2.48E+00 3.34E+01 3.01E+02 5.58E+00 2.58E+00 3.58E+</td> <td>/molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s /s</td> <td>titled fitted</td> <td>Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of p-Raf Dephosphorylation of pp-MEK Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of p-ERK by DUSP</td>	1117/38/y42 1177/43 1187/447y45 1187/447y45 1187/447y45 1187/47 1207/47y48 1207/47y48 1207/47y48 1207/49 1207/49 1217/51 1227/37y50 1227/52 1227/52 1227/52 1227/54 1227/55 1237/55	k117 kc17 kc18 kc18 kc18 kc18 k120 kc20 kc20 kc21 kc21 kc21 kc21 kc22 kc22 kc22 kc22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.75E-01 1.47E+02 9.98E+01 3.70E-06 2.42E+02 6.89E-04 2.98E+00 2.48E+00 3.34E+01 3.01E+02 5.58E+00 2.58E+00 3.58E+	/molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s /s	titled fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of p-Raf Dephosphorylation of pp-MEK Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of p-ERK by DUSP
57 58 59 60 61 62 63 64 65 66 67 68 69 70 77 77 77 77 77 78 9 80	pp-MEK + p-ERK >> pp-MEK + pERK >> pp-MEK + pERK >> pp-MEK + pERK >> psK + pp-ERK > RSK - pp-ERK > PRISK + PP-ERK > PRISK + PP-ERK > PRISK + PP-ERK > PRISK + PAR > PRISK + PRERK > PRISK + PAR > PRISK + Pased > Pased - pp-MEK + Pased > Pased + pp-MEK + Pased > PUSP pp-ERK + > > > > PUSP pp-ERK + DUSP > > > PUSP pp-ERK + DUSP > > > PUSP pp-ERK + > > > > PUSP pp-ERK + DUSP > <t< td=""><td>H177/38'y42 H177/43 H179/44 K177/43 K187/44/y45 K187/46 K187/46 K187/46 K1207/47/48 H2207/49 K2207/49 K2217/61 K217/61 K217/61 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/954 K227/954 K227/955 K2247/955 K2247/955</td><td>k117 kr17 k118 kr18 kr18 kr18 kr20 kr20 kr20 kr21 kr21 kr21 kr21 kr21 kr22 kr22 kr23 kr23 kr24 kr24 kr24</td><td>1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.72E+01 1.72E+01 3.74E+01 3.74E+02 6.98E+00 3.24E+02 6.98E+00 2.42E+02 5.98E+00 2.43E+04 3.34E+01 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.35E-</td><td>/molecules/s /s /s /s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s</td><td>titled fitted</td><td>Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of P-Raf Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of p-ERK by DUSP</td></t<>	H177/38'y42 H177/43 H179/44 K177/43 K187/44/y45 K187/46 K187/46 K187/46 K1207/47/48 H2207/49 K2207/49 K2217/61 K217/61 K217/61 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/97/950 K227/954 K227/954 K227/955 K2247/955 K2247/955	k117 kr17 k118 kr18 kr18 kr18 kr20 kr20 kr20 kr21 kr21 kr21 kr21 kr21 kr22 kr22 kr23 kr23 kr24 kr24 kr24	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.72E+01 1.72E+01 3.74E+01 3.74E+02 6.98E+00 3.24E+02 6.98E+00 2.42E+02 5.98E+00 2.43E+04 3.34E+01 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.34E+04 3.35E-	/molecules/s /s /s /s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s	titled fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of P-Raf Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of p-ERK by DUSP
57 58 59 60 61 62 63 64 65 66 67 68 69 70 77 73 74 75 77 77 78 980 ans	pp-MEK + p-ERK >> pp-MEK + pERK >> pp-MEK + pERK >> pp-MEK + pERK >> psK + pp-ERK >> RSK - pp-ERK >> PRSK + paceRK >> PRSK + paceRK >> PRSK - pp-ERK >> Pasad_p-Pal >> Pasad_p-Pal >> Pasad_p-MEK + Pasa4 > Pasad_p-MEK > >> PuEK + Pasa4 > Pasad_p-MEK > > PuEK + Pasa4 > Pasa4_p-MEK > > PuEK + Pasa4 > Pasa4_p-MEK > > PuEK + Pasa4 > PuEK + Pasa4 > PuEK + Pasa4 > PuEK + Pasa4 > PuEK + Pa	H17739742 H17743 H17743 H18744745 K18744745 K18746 H187474745 H20734748 H20734748 H20734748 H20749 H20734748 H20749 H21751 K21751 K21751 K21751 K21751 K2273750 H2273750 H2273750 H227352 H23744753 K223754 K223754 K223754 K223754 K223754 K223754 K223755 K224755	k117 kr17 kr18 kr18 kr18 kr20 kr20 kr20 kr20 kr21 kr21 kr21 kr21 kr21 kr22 kr22 kr23 kr23 kr24 kr24 kr24 kr24 kr24	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.47E+02 9.98E+01 3.70E-06 2.42E+02 4.24E+02 4.24E+02 5.98E+00 2.42E+03 3.24E+	/molecules/s /s /s /s /s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /s /molecules/s /s /s /s /s /s /s /s /s /s /s /s /s	itted fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of PSK Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of pp-ERK by DUSP
757 758 759 760 761 762 763 766 766 766 766 766 766 770 771 772 773 774 775 776 777 778 779 780 779 780	pp-MEK → p-ERK >> pp-MEK → pERK >> pp-MEK → pERK >> pp-MEK → pERK >> RSK → pp-ERK > RSK → pp-ERK > RSK → pp-ERK > PR36 → p-Rat + Pased > Pased → PASEK > PASEK → PASEK > Pased → PASEK > PASEK → PASEK > PASEK → PASEK > PASEK → PASEK > PASEK → PASEK → PASEK + PASES PASEK → PASEK →	H177/93'Y42 H177/93 Kc177/94 Kc177/94 Kc187/94 Kc187/94 Kc187/94 Kc187/94 Kc187/94 Kc207/94 Kc207/94 Kc207/94 Kc207/94 Kc207/94 Kc207/95 Kc207/95 Kc207/95 Kc27	k117 k117 k118 k118 k19 k20 k20 k20 k20 k21 k21 k21 k22 k22 k22 k22 k23 k22 k22 k22 k22 k22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+001 1.12E+01 1.72E+02 1.72E+02 1.74E+02 2.42E+03 3.70E-06 2.42E+02 5.89E+00 2.42E+02 5.88E+00 2.43E+04 3.51E-05 2.18E+00 2.07E+01 2.42E+04	/molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s	titled fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of RSK Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of pp-ERK by DUSP Synthesis of c-Fos promoted by both pp-ERK- and p-RSK [1]
57 58 59 60 61 62 66 66 66 66 66 66 66 66 66 66 77 77 77	pp-MEK + p-ERK >> pp-MEK + pERK >> pp-MEK + pERK >> pp-MEK + pERK >> psK + pp-ERK >> RSK - pp-ERK >> RSK - pp-ERK >> PRIS + pp-ERK >> RSK - pp-ERK >> PRIS + pp-ERK >> PRIS + pp-ERK >> PRIS + pp-ERK >> PRIS + pp-ERK >> Passd - p-All + Pass3 > Passd - pp-MEK >> Passd - pp-MEK >> PAEK + Pass4 > Pass4 - pp-MEK >> Pass4 - pp-MEK >> Pass4 - pp-ERK > DUSP pp-ERK > DUSP pp-ERK > PUSP + PERK > DUSP pp-ERK > PUSP + SerK + DUSP > DUSP pp-ERK > DUSP pp-ERK > DUSP pp-ERK > PoleK + R & pp-ENK > <td< td=""><td>H17'/39'y42 H17'y43 Kc17'y43 Kc17'y43 Kc18'y46 Kc18'y46 Kc18'y46 Kc18'y46 Kc20'y49 Kc20'y49 Kc20'y49 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc22'y52 Kc22'y52 Kc22'y52 Kc22'y54 Kc23'y54 Kc23'y54 Kc23'y54 Kc23'y54 Kc23'y54 Kc23'y54 Kc23'y55 Kc24</td><td>k117 kr17 kr18 kr18 kr18 kr20 kr20 kr20 kr20 kr20 kr21 kr21 kr21 kr21 kr22 kr22 kr22 kr22</td><td>1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.47E+02 9.98E+01 3.70E-06 9.98E+01 3.70E-06 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+04 2.55E-02 2.18E+00 2.42E+04 2.42E+04 2.42E+04 2.42E+04 2.56E+12 1.51E+14 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 3.55E+</td><td>/molecules/s /s /s /molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s</td><td>titled fitted fi</td><td>Phosphorylation of p.EHK by MEK Phosphorylation of P.SK by ERK Dephosphorylation of p.RK Dephosphorylation of p.MEK Dephosphorylation of p.MEK Dephosphorylation of p.ERK by DUSP Dephosphorylation of p.ERK by DUSP Synthesis of c-Fos promoted by both pp.ERK- and p.RSK [1] Dependence of the For</td></td<>	H17'/39'y42 H17'y43 Kc17'y43 Kc17'y43 Kc18'y46 Kc18'y46 Kc18'y46 Kc18'y46 Kc20'y49 Kc20'y49 Kc20'y49 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc22'y52 Kc22'y52 Kc22'y52 Kc22'y54 Kc23'y54 Kc23'y54 Kc23'y54 Kc23'y54 Kc23'y54 Kc23'y54 Kc23'y55 Kc24	k117 kr17 kr18 kr18 kr18 kr20 kr20 kr20 kr20 kr20 kr21 kr21 kr21 kr21 kr22 kr22 kr22 kr22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.47E+02 9.98E+01 3.70E-06 9.98E+01 3.70E-06 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+04 2.55E-02 2.18E+00 2.42E+04 2.42E+04 2.42E+04 2.42E+04 2.56E+12 1.51E+14 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 2.42E+04 2.55E+12 3.55E+	/molecules/s /s /s /molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s	titled fitted fi	Phosphorylation of p.EHK by MEK Phosphorylation of P.SK by ERK Dephosphorylation of p.RK Dephosphorylation of p.MEK Dephosphorylation of p.MEK Dephosphorylation of p.ERK by DUSP Dephosphorylation of p.ERK by DUSP Synthesis of c-Fos promoted by both pp.ERK- and p.RSK [1] Dependence of the For
757 758 759 760 761 763 764 766 766 766 770 771 772 773 774 775 776 777 778 779 780 778 779 780 778 779 780 778 779 780 778 779 780	pp-MEK + pERK → pp-MEK + pp-ERK pp-MEK _ pERK → pp-MEK + pp-ERK RSK + ppERK → pp-MEK + pp-ERK RSK + ppERK → PRK PRSK → PRK → PP-RK PRSK → PRSK → PRSK PRSK → PRSK → PRSK PRSK → PRSK → PRSK Pasad _ p-Rat → Paat + Pasa3 Pasad _ p-Rat → Paat + Pasa3 Pp-MEK + Pasa4 Pasa4 _ p-MEK → pp-MEK + Pasa4 Pasa4 _ p-MEK → pp-MEK + Pasa4 Pasa4 _ p-MEK → pp-MEK + Pasa4 Pasa4 _ p-MEK → pp-ERK + Pasa4 Pasa4 _ p-MEK → pp-ERK + Pasa4 Pp-ERK + DUSP DUSP _ pp-ERK → pp-ERK + DUSP	H177/93'Y42 H177/93'Y42 H177/94 H187/94/Y45 H187/94 H187/94 H207/94/94 H207/9	k117 k117 k118 k118 k18 k19 k120 k120 k120 k121 k21 k22 k121 k22 k121 k22 k122 k1	1.78E-02 1.50E+01 1.01E+02 5.20E-05 2.52E-05 2.52E+05 2.52E+01 1.52E+01 1.52E+01 1.52E+01 1.47E+02 9.96E+01 3.70E-06 2.42E+03 2.42E+02 5.98E+00 2.43E+04 2.96E+02 5.51E-05 2.42E+04 2.43E+04 2.55E+12 1.91E-04 2.55E+12 1.91E-04 1.91E-	/molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s molecules/s molecules/s molecules/s /s	titled fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of p-MEK Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of pp-ERK by DUSP Synthesis of c-Fos promoted by both pp-ERK- and p-RSK [1] Degradation of c-Fos
57 58 59 60 66 66 66 66 66 66 66 66 66 66 66 70 77 77 77 77 77 77 77 77 77 77 77 77	pp-MEK → pERK >> pp-MEK → pERK >> pp-MEK → pERK >> pp-MEK → pERK >> RSK → pp-ERK > RSK → pp-ERK > RSK → pp-ERK > RSK → pP-ERK > PAB4 + Pasel > Pasel → PAR + Pasel > PUSP → PER + DUSP > PUSP → PER + S > <	H17'/93'Y42 H17'Y43 Kc17'Y43 Kc17'Y43 Kc18'Y46 Kc18'Y46 Kc18'Y46 Kc18'Y46 Kc20'Y49 Kc20'Y49 Kc20'Y49 Kc20'Y49 Kc21'Y51 Kc21'Y51 Kc21'Y51 Kc21'Y51 Kc21'Y51 Kc21'Y51 Kc21'Y51 Kc21'Y51 Kc21'Y51 Kc21'Y55 Kc21	k117 kr17 kr18 kr18 kr18 kr20 kr20 kr20 kr21 kr21 kr21 kr22 kr22 kr22 kr22 kr22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.75E+01 1.75E+01 3.70E-03 3.70E-04 3.70E-	/molecules/s /s /s /molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s	titled fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of RSK by ERK Dephosphorylation of p-MEK Dephosphorylation of p-MEK Dephosphorylation of p-ERK by DUSP Dephosphorylation of p-ERK by DUSP Synthesis of c-Fos promoted by both p-ERK- and p-RSK [1] Degradation of c-Fos Basal synthesis of PHLDA1 Synthesis of PHLDA1 Synthesis of PHLDA1
57 58 58 59 60 66 66 66 66 66 66 66 66 66 66 66 66	pp-MEK → pERK → pp-MEK + pp-ERK pp-MEK → pERK → pp-MEK + pp-ERK RSK → pp-ERK → pp-MEK + pp-ERK RSK → pp-ERK → RSK + pp-ERK P-RSK → RSK + pp-ERK P-RSK → RSK + pp-ERK P-RSK → RSK → P-R3 + Pase3 Pase4 pp-MEK → pp-MEK + Pase4 Pase4 pp-MEK → pp-ERK + DUSP p=ERK + DUSP DUSP pp-ERK → pp-ERK +	ht17',93'y42 ht17'y43 ht17'y44 ht17'y44 ht18'y44'y45 ht18'y44'y45 ht18'y46 ht20'y44'y48 ht20'y44'y48 ht20'y49 ht20'y49 ht21'y51 ht21'y51 ht22'y37'y50 ht22'y52 ht23'y44'y53 ht23'y54 ht23'y55 ht23'y54 ht23'y55 ht23'y56 ht23'y57	k117 kr17 kr18 k118 k19 k120 kc20 kc20 kc20 kc21 kc21 kc21 kc21 kc21 kc21 kc22 kc22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.47E+02 9.98E+01 3.70E-06 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+04 2.98E+00 2.43E-04 3.94E+01 3.01E+02 5.58E+05 2.18E+00 2.42E+04 2.59E+12 1.91E-04 1.91E-	/molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s	titled fitled	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of RSK Deactivation of p-Raf Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of p-ERK by DUSP Synthesis of c-Fos promoted by both pp-ERK- and p-RSK [1] Degradation of c-Fos Basal synthesis of PHLDA1 Synthesis of PHLDA1 Synthesis of PHLDA1 Synthesis of PHLDA1
157 158 159 160 162 162 163 164 165 166 167 171 172 177 177 177 177 177 177 177 17	pp-MEK + pERK >> pp-MEK + pERK >> pp-MEK + pERK >> pp-MEK + pERK >> psK + pp-ERK > RSK , pp-ERK > PRSK + pp-ERK > Pasd - pp-MEK + Pase3 > Pasd + pp-MEK + Pase4 > Pase4 - pp-MEK + Pase4 > PuEK + Pase4 - pp-MEK + Pase4 > PuEK + Pase4 - pp-MEK + Pase4 > PuEK + pp-PERK - > pp-ERK + DUSP > DUSP - pERK - > pp-ERK + DUSP > DUSP - pERK - > p-ERK + DUSP > DUSP	H177/39'y42 H177/43 Kc177/43 Kc177/43 Kc187/44 Kc187/46 Kc187/46 Kc187/46 Kc207/49 Kc207/49 Kc207/49 Kc217/61 Kc217/61 Kc217/61 Kc217/61 Kc217/61 Kc217/64 Kc237/56 Kc237/57 Kc237/57 Kc237/57 Kc237/57 Kc237/57 Kc237/57 Kc237/57 Kc23	k117 k117 k118 k118 k18 k18 k20 k20 k20 k22 k22 k22 k22 k22 k22 k22	1.78E-02 1.50E+01 1.50E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.72E+01 1.72E+01 1.72E+01 3.77E+06 3.77E+06 3.77E+06 3.77E+06 3.77E+06 3.78E+00 2.42E+02 5.88E+00 2.42E+04 2.55E+02 2.42E+04 2.55E+02 1.92F-04 1.14E-08 1.15F-04 1.14E-08 1.15F-04 1.14E-08 1.16F-04 1.16F-	/molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s molecules/s /s molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /s /s /s /s /s /s /s /s /s /s	titled fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of RSK Deadtivation of p-Raf Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of pp-ERK by DUSP Synthesis of c-Fos promoted by both pp-ERK- and p-RSK [1] Degradation of c-Fos Basal synthesis of PHLDA1
57 558 59 60 661 662 663 664 666 666 666 666 666 666 666 666	pp-MEK → pERK → pp-MEK + pp-ERK pp-MEK → pERK → pp-MEK + pp-ERK RSK → pp-ERK → pp-MEK + pp-ERK RSK → pp-ERK → RSK + pp-ERK P-RSK → RSK + pp-ERK P-RSK → RSK + pp-ERK P-RSK → RSK + pp-ERK P-RSK → PAR + Pase3 P-RSK → PAR + Pase3 P-RSK → pp-RSK → pp-MEK + Pase4 Pase4 → PMEK + Pase4 Pase4 → PMEK → pp-MEK + Pase4 Pase4 → PMEK → pp-ERK + DUSP DUSP µp-ERK → pp-ERK → pP-ERK → DUSP DUSP µp-ERK → pP-ERK → pP-ERK → DUSP DUSP µp-ERK → pP-ERK → PP-ERK → PF-PF-FK → PF-PF-FK → PF-PF-FK → PF-PF-FK → PF-PF-FK → PF-FK → PF-F	H17'/39'y42 H17'y43 H17'y43 Kc17'y43 Kc17'y45 Kc18'y46 Kc18'y46 Kc18'y46 Kc20'y49 Kc20'y49 Kc20'y49 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc22'y52 Kc22'y52 Kc23'y54 Kc23'y56 Kc23'y57 Kc23'y57 Kc23'y57 Kc23'y57 Kc23'y57 Kc23'	k177 kr17 kr18 kr18 kr18 kr20 kr20 kr20 kr21 kr21 kr21 kr21 kr21 kr22 kr22 kr22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.75E+01 1.47E+02 9.88E+01 3.70E-06 9.88E+01 3.70E-06 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+03 2.42E+04 2.55E-05 2.18E+00 2.75E+01 2.42E+04 2.55E-05 2.18E+00 2.75E+01 1.15E-04 1.15E-	/molecules/s /s /molecules/s /molecules/s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s molecules/s /molecules/s	titled fi	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of RSK Deactivation of p-Raf Dephosphorylation of pp-MEK Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of p-ERK by DUSP Synthesis of c-Fos promoted by both pp-ERK- and p-RSK [1] Degradation of c-Fos Basal synthesis of PHLDA1 Degradation of PHLDA1 D
157 158 159 160 162 163 166 166 166 166 166 170 171 172 173 174 175 177 178 181 182 183 181 182 183 183 185 183 183 183 183 183 183 183 183 183 183	pp-MEK → p-ERK → pp-MEK + p-ERK pp-MEK → pERK → pp-MEK + pp-ERK RSK + pp-ERK → pp-MEK + pp-ERK RSK + pp-ERK → RSK + pp-ERK P-RSK → PR-RSK + pp-ERK P-RSK → PR-RSK + pp-ERK P-RSK → PR-RSK + pp-ERK P-RSK → pp-RsK + pp-RsK Pasad p-Rat → pp-Rat + Pasad pp-MEK + Pasad Pp-MEK + Pasad Pp-MEK + Pasad Pp-MEK + Pasad Pp-MEK + Pasad Pp-ERK → pp-MEK + Pasad Pasad pp-MEK → pp-ERK + DUSP DUSP pp-ERK → p-ERK + DUSP DUSP pp-ERK → p-ERLAT JUSP DUSP pp-ERK → p-ERLAT JUSP DUSP pp-ERK → p-ERLAT JUSP DUSP pp-ERK → p-ERLAT JUSP DUSP pp-ERK → pHDLAT Juspthesis C+fos & p-ALAT synthesis PHGR_pt-EX2 dpHRGR_pt-ERb22 > PTPN synthesis PTPN → disgradation	ht17',93'y42 ht17',94' ht17',94' ht17',94' ht18',94'y45 ht18',94'y45 ht20',94'y48 ht20',94'y48 ht20',94'y48 ht20',94'y48 ht20',94'y48 ht20',94'y48 ht20',94'y48 ht20',94'y48 ht20',94'y48 ht21',95' ht22',95' ht22',95' ht22',95' ht22',95' ht22',95' ht23',95' ht23',95' ht23',95' ht24',95	k177 kc17 kc18 kr18 kr18 kr20 kc20 kc20 kc20 kc21 kc21 kc21 kc21 kc21 kc22 kc22 kc22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+001 1.12E+01 1.21E+02 1.21E+02 1.21E+02 1.21E+02 2.42E+03 3.70E-06 2.42E+02 5.88E+00 2.42E+02 5.88E+00 2.42E+02 5.88E+00 2.42E+04 2.42E+04 1.31E+05 1.31E	/molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s molecules/s /s /s /s /s /s /s /s /s /s /s /s /s	fitted fitted	Phosphorylation of p-EHK by MEK Phosphorylation of RSK by ERK Dephosphorylation of RSK Depote Phosphorylation of pp-MEK Dephosphorylation of pp-MEK Dephosphorylation of pp-ERK by DUSP Dephosphorylation of pp-ERK by DUSP Synthesis of c-Fos promoted by both pp-ERK- and p-RSK [1] Degradation of c-Fos Basal synthesis of PHLDA1 Degradation of PHLDA1 Synthesis Of PHLDA1
57 58 59 66 66 66 66 66 66 66 66 66 6	pp-MEK → DERK → pp-MEK + pp-ERK pp-MEK → DERK → pp-MEK + pp-ERK RSK → pp-ERK → pp-MEK + pp-ERK RSK → pp-ERK → RSK + pp-ERK P-RSK → RSK + pp-ERK P-RSK → RSK + pp-ERK P-RSK → RSK + pp-ERK P-RSK → P-RSK → p-Rst + Pase3 Pase3, p-Rst → P-Rst + Pase3 Pase3, pp-MEK → pp-MEK + Pase4 Pase4, pp-MEK → pp-ERK + DUSP DUSP pp-ERK → p-ERK → p-ERK + DUSP PFENK → DUSP primesis -Fos & p-Att → p-Att A + p-ErbR2 → PTM synthesis P-FEK → DUSP py-thesis	H17'/39'y42 H17'y43 Kc17'y43 Kc17'y43 Kc18'y46 Kc18'y46 Kc18'y46 Kc18'y46 Kc20'y49 Kc20'y49 Kc20'y49 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc21'y51 Kc22'y52 Kc23'y52 Kc23'y54 Kc23'y54 Kc23'y55 Kc23	k177 kr17 kr18 kr18 kr18 kr20 kr20 kr21 kr21 kr21 kr22 kr22 kr22 kr22 kr22	1.78E-02 1.50E+01 1.01E+02 5.20E-05 3.25E+02 4.08E+00 1.12E+01 1.47E+02 9.8E+01 3.70E+06 9.8E+00 2.42E+02 2.42E+02 2.42E+02 2.42E+02 2.42E+02 2.42E+02 2.42E+02 2.42E+02 2.42E+04 2.42E+04 2.51E+05 2.42E+04 2.51E+05 2.42E+04 2.51E+05 2.42E+04 2.52E+02 1.51E+04 1.52E+04 2.52E+02 3.52E+02	/molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /molecules/s /s /s /molecules/s /s /s /s /molecules/s /s /s /s /molecules/s /s /s /molecules/s /s /s /s /s /s /s /s /s /s /s /s /s	htted fit	Phosphorylation of p-EHK by MEK Phosphorylation of PSK by ERK Dephosphorylation of PSK Dephosphorylation of p-MEK Dephosphorylation of p-MEK Dephosphorylation of p-ERK by DUSP Dephosphorylation of p-ERK by DUSP Synthesis of c-Fos promoted by both pp-ERK- and p-RSK [1] Degradation of c-Fos Basal synthesis of PHLDA1 Synthesis of PHLDA1 Synthesis of PHLDA1 Synthesis of PTPN promoted by both pARG_pErbB2 dimer and tetramer Degradation of PTPN Basal synthesis of DTPN

	Table S7.	Initial	concentration	of	molecules in	the	expanded	mode
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Symbol	Species	Molecules/cell	Reference
HRG	Concentration of HRG	10 (uM)	Experimental condition in this study
y1	HRGR	10000	We regard ErbB3 as HRG receptor (HRGR) in this study. Number of ErbB3 receptors is below 10,000 molecules per cell [1].
y2	HRGR_ErbB2	0	
y3	HRG:HRGR	0	
y4	HRG:HRGR_ErbB2	0	
y5	pHRGR_pErbB2	0	
y6	(pHRGR_pErbB2)2	0	
y7	PI3K	669000	fitted
y8	pE2pE3_PI3K	0	
y9	(pE2pE3)2_PI3K	0	
y10	active_PI3K	0	
y11	PIP2	7840000	fitted
y12	active_PI3K_PIP2	0	
y13	PIP3	0	
y14	PDK1	1520000	fitted
y15	PIP3_PDK1	0	
y16	p-PDK1	0	
y17	Akt	338000	fitted
y18	p-PDK1_Akt	0	
v19	pAkt	0	
v20	Pase1	213000	fitted
v21	Pase1 PI3KA	0	
y v22	PTEN	68300	fitted
v23	PTEN PIP3	0	
v24	Pase2	674000	fitted
v25	Pase2 p-PDK1	0	
v26	PP2A	2370	fitted
v27	PP2A p-Akt	0	
v28	RasGDP	250000	400 nM per cell [2]
v29	pE2pE3 RasGDP	0	···· ··· ··· ··· [-]
v30	(pE2pE3)2 RasGDP	0	
v31	RasGTP	0	
v32	Raf	8000	13 nM per cell [2]
v33	RasGTP Raf	0	
v34	p-Raf	0	
v35	MEK	850000	1400 nM per cell [2]
v36	p-Raf MEK	0	
v37	p-MEK	0	
v38	p-Raf MEKP	0	
v39	pp-MEK	0	
v40	ERK	600000	960 nM per cell [2]
v41	pp-MEK ERK	0	
v42	p-ERK	0	
v43	pp-MEK p-ERK	0	
v44	pp-ERK	0	
v45	RSK	498000	fitted
v46	RSK pp-FBK	0	
y47	p-BSK	0	
v48	Pase3	5930	fitted
v49	Pase3 p-Raf	0	
v50	Pase4	1920000	fitted
v51	Pase4 pp-MEK	0	····· • •
v52	Pase4 p-MFK	0	
v53	DUSP	10000	fitted
y54	DUSP nn-FRK	0	intod
y55	DUSP n-FRK	õ	
y56	c-Fos	0 0	
y57	PHI DA1	60000	fitted
v58	Phosphatase	0	intou
v59	ErbB2	8000	Number of ErbB2 receptors is below 10,000 molecules per cell [1]
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[1] Zhang, Q. et al., Proc. Natl. Acad. Sci. USA 109, 13237–13242 (2012).

[2] Fujioka, A. et al., J. Biol. Chem., 281, 8917–8926 (2006).

Table S8. CV of molecules in the expanded model

Species	CV of protein concentrations (%)	Reference
HRGR (ErbB3)	31	
ErbB2	42	• • • • • •
Akt	39	(Fig. 3D)
ERK	35	(Tig. 5D)
PHLDA1	60	
Others	35	Typical order [1, 2]

[1] Meyer, R. et al., Frontiers in physiology, 3, 451-451 (2011).

[2] Spencer, S. et al., Nature 459.7245, 428-432 (2009).

Table S9. Rank correlations in the expanded model

Combination	Rank correlation	Reference
HRGR(ErbB3)-PHLDA1	0.13	
ErbB2_PHLDA1	0.27	Measured in this
ERK-PHLDA1	0.15	(Fig. 3F)
Akt-PHLDA1	0.14	(1.9.01)