

Supporting Information

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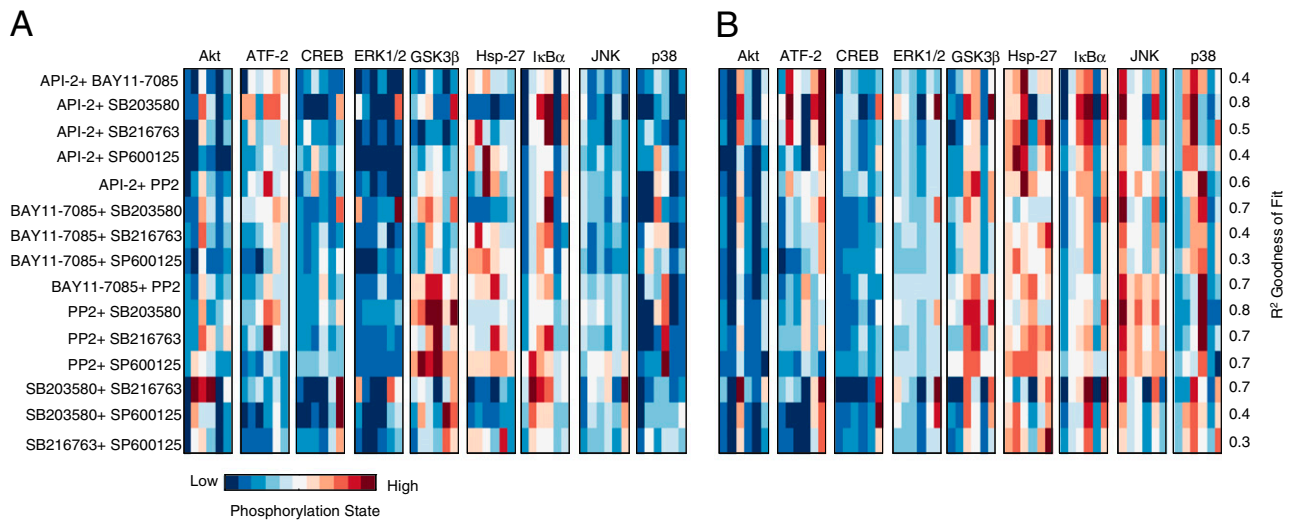


Fig. S1. Paired inhibitor combinations perturb CVB3-induced phosphorylation signatures nonadditively. (A) Measured inhibitor pairs were reprinted from Fig. 1 and compared with (B) an additive model, in which single inhibitor time courses from Fig. 1 were used to predict paired inhibitor signatures by adding the net perturbation of each inhibitor compared with the DMSO control. Differences between the measured and modeled signatures were evaluated by R^2 goodness of fit (Right). The median R^2 value was 0.6.

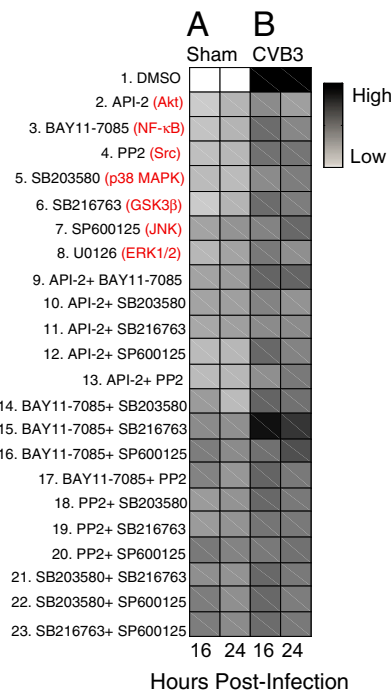


Fig. S2. Single and paired inhibitors specifically inhibit CVB3-induced cardiotoxicity. Cell death as measured by MTS assay is shown for (A) sham-infected cardiomyocytes or (B) CVB3-infected cardiomyocytes at 16 and 24 h p.i. HL1 cells were pretreated and infected as described in Fig. 1. Data are presented as the mean of three independent replicates. Cell death was normalized to the DMSO-treated control.

Table S2. Scientific support for the CVB3 partial correlation network shown in Fig. 4B

Edge	Partial correlation	Reported interaction	Ref(s).
Hsp-27-CREB	0.5	Direct phosphorylation of Hsp-27 and CREB by RSK2	(1)
JNK-I κ B α	-0.5	Inhibition of JNK activation by NF- κ B-mediated induction of <i>GADD45B</i> and <i>XIAP</i>	(2, 3)
p38-I κ B α	0.5	p38-mediated phosphorylation of MSK1 promotes NF- κ B function, which induces <i>IKBA</i>	(4, 5)
ERK-CREB	0.5	Direct phosphorylation of CREB through ERK-mediated phosphorylation of RSK	(6)
Akt-GSK3 β	0.4	Direct phosphorylation of GSK3 β by Akt	(7)
JNK-ATF-2	-0.3	Direct phosphorylation of ATF-2 by JNK (negative correlation unexplained)	(8)
I κ B α -ATF-2	-0.3	Negative correlation unexplained	—
GSK3 β -I κ B α	0.3	GSK3 β required for normal NF- κ B function, which induces <i>IKBA</i>	(9–11)
Akt-I κ B α	0.3	Direct phosphorylation of I κ B α through Akt-mediated phosphorylation of IKK	(12, 13)
p38-Hsp-27	0.3	Direct phosphorylation of Hsp-27 through p38-mediated phosphorylation of MK2	(14, 15)

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