#### **Supplementary Information**

#### (11 Figures and 1 supplementary method)

### Predicting chemotherapeutic drug combinations through gene network profiling

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#### **Supplementary Figures and Supplementary Method**

**Supplementary Figure 1** Spotting of doxorubicin resistance (DXR) strains obtained with indicated concentrations of hydroxyurea (HU).

**Supplementary Figure 2** Spotting of doxorubicin resistance (DXR) strains obtained with indicated concentrations of methyl methanesulfonate (MMS).

**Supplementary Figure 3** Spotting of doxorubicin resistance (DXR) strains obtained with indicated concentrations of camptothecin (CPT).

**Supplementary Figure 4** Spotting of doxorubicin resistance (DXR) strains obtained with indicated concentrations of thiabendazole (TBZ).

**Supplementary Figure 5** Spotting of doxorubicin resistance (DXR) strains obtained with indicated concentrations of cisplatin.

**Supplementary Figure 6** Spotting of doxorubicin resistance (DXR) strains obtained with indicated concentration of suberoylanilide hydroxamic acid (SAHA).

**Supplementary Figure 7** Derivation of sensitivity scores (s-scores) from cell growth phenotypes grown on a series of drug concentrations. (a) Quantitation of the fold sensitivity from the 10-fold serially diluted drug plates. (b) Formula expressing the logarithmic transformation of the mean fold sensitivity relative to the growth of cells on non-drug-treated plates. (c) Schematic representation of the interpretation of the s-score values. A value of 0 is taken as no sensitivity, a negative s-score represents hypersensitivity, and a positive value means resistance.

**Supplementary Figure 8** Serial dilution of wild-type (WT) prototrophic fission yeast strains of mating type  $h^+$  (975) and  $h^-$  (972) on 0, 15, 30, 75 µg/ml doxorubicin alone or in conjunction with 0.01% methyl methanesulfonate (MMS), 8 µg/ml thiabendazole (TBZ), 2

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mM hydroxyurea (HU), 8 µM camptothecin (CPT), 1.2 mM cisplatin, 5 mM suberoylanilide hydroxamic acid (SAHA) or with 1.2 mM cisplatin and 5 mM SAHA. These concentrations were selected as they did not significantly reduce WT cell viability. Cell growth was assessed on days 3 and 7 after spotting onto drug plates.

**Supplementary Figure 9** DXR mutants exhibit hypersensitivity towards the triple combination of cisplatin, SAHA and doxorubicin. WT,  $\Delta rhp51$ ,  $\Delta rav1$ ,  $\Delta vps35$ ,  $\Delta caf1$  and  $\Delta tim11$  were 10-fold serially diluted and spotted onto media containing 0, 15, 30, 75 µg/ml doxorubicin alone or in combination with 1.2 mM cisplatin, 5 mM suberoylanilide hydroxamic acid (SAHA). Cell growth was analyzed on days 3 and 7 after drug treatment.

**Supplementary Figure 10** Sensitization of human cervical carcinoma (HeLa) cells to doxorubicin via concurrent treatment with cisplatin and suberoylanilide hydroxamic acid (SAHA). (a) Cells were co-treated with varying concentrations of cisplatin (halving dilutions from 100  $\mu$ M to 0) in the presence of 10, 15, or 25  $\mu$ M SAHA, or 0.1, 1 or 5  $\mu$ M doxorubicin or with a triple combination (10  $\mu$ M SAHA constant). (b) Dose response effect on the viability of HeLa cells was analyzed following treatment with varying concentrations of cisplatin alone (blue), in combination with 0.1  $\mu$ M doxorubicin (green) or 10  $\mu$ M SAHA (red), or 0.1  $\mu$ M doxorubicin and 5  $\mu$ M SAHA (purple). (c) Similar to (b) except 1  $\mu$ M doxorubicin was used.

**Supplementary Figure 11** Human non-cancerous embryonic kidney (HEK293) cells did not show cumulative cell killing in triple combination of doxorubicin, cisplatin and suberoylanilide hydroxamic acid (SAHA). (a) Cells were co-treated with varying concentrations of cisplatin (halving dilutions from 100  $\mu$ M to 0) in the presence of 5, 50, 100  $\mu$ M SAHA, or 0.06, 0.15 or 1  $\mu$ M doxorubicin or with a triple combination (5  $\mu$ M SAHA constant). (b) Dose response effect on viability of HEK293 cells were analyzed after treating

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with varying concentrations of cisplatin alone (blue), in combination with 0.1  $\mu$ M doxorubicin (green) or 10  $\mu$ M SAHA (red), or 0.06  $\mu$ M doxorubicin and 5  $\mu$ M SAHA (purple). (c) Similar to (b) except 0.15  $\mu$ M doxorubicin was used.

Supplementary Materials and Methods Chemical synthesis of SAHA

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∆rsc4	<ul> <li>●●●● </li> <li>●●● </li> <li>●● </li> <li>●● </li> <li>●</li> <li>●</li> </ul>	<ul> <li>• • • • • •</li> <li>• • • • • • • • • • • • • • • • • • •</li></ul>	<ul> <li></li></ul>	3 7
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Hydroxyurea (mM)	0	2	4	Day
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Methyl methanesulfonate (%)	0	0.001	0.002	0.005	0.01	0.02	D
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∆apl6	• • • • • • • • • • • • • • • • • • •	© © © . •	© © ⊗ © © © ⊗ <sup>©</sup> •	© © © © © © © © © © © ©	<ul> <li></li></ul>	© © © © . © © & ‡ .	3 7
Δarp42	<b>NG &amp; S</b> ect. (1) NG <b>&amp; S</b> ect. (1)	<b>\</b> <b>\</b> <b>\</b> <b>\</b> <b>\</b> <b>\</b> <b>\</b> <b>\</b> <b>\</b> <b>\</b>	<b>\</b>	<b>. 69</b> @ 3 4	\ <b>@</b> @ ∲	©⊜∯:	3 7
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Methyl methanesulfonate (%)	0	0.001	0.002	0.005	0.01	0.02	Dav
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Methyl methanesulfonate (%)	0	0.001	0.002	0.005	0.01	0.02	Dav
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Camptothecin (µM)	0	6	8	10	12	Day
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Camptothecin (µM)	0	6	8	10	12	Day
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∆SPAC2F3.11	●●●☆☆ <i>↓</i> ●●●☆☆ <b>↓</b>	<ul> <li>•</li> <li>•</li></ul>	<ul> <li></li> <li></li></ul>	•••• ••••	<b>O</b> S S S S S S S S S S S S S S S S S S S	3 7
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Camptothecin (µM)	0	6	8	10	12	Day
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Thiabendazole (µg/ml)	0	8	10	Day
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Thiabendazole (µg/ml)	0	8	10	Day
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∆coq3	00000000000000000000000000000000000000	• • • • •	••• •••	3 7
∆coq4	10000000 10000000000000000000000000000	<ul> <li></li></ul>	0000 00000	3 7
∆coq6		<ul> <li>Image: Image: Ima</li></ul>	<b>.</b>	3 7
Δcoq7	\$\$\$\$\$	● ● <sup>●</sup> <sup>●</sup> <sup>●</sup>	• @ @ @ ^ • @ @ & A	3 7
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Δcox19	. • • • • *	<ul> <li></li> <li><th>••• •••</th><th>3 7</th></li></ul>	••• •••	3 7
Δcox6	••••	0003 0003	00000 00000000000000000000000000000000	3 7
Δcph2	<b>6</b> (1) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2	© © 3 3	000 00 00 0000 00	3 7
∆csn1	<b>.</b> • • • • • • • • • • • • • • • • • • •		80 80	3 7
∆csn2	00% 00% 00%	● (a) (c) (k) ● (a) (c) (k)	<ul> <li>.</li> <li>.</li></ul>	3 7
∆ctp1	<ul> <li>● 36</li> <li>○</li> <li>● 36</li> <li>○</li> </ul>		<ul> <li>(6)</li> <li>(6)</li> <li>(6)</li> <li>(6)</li> <li>(7)</li> <li>(7)</li></ul>	3 7
∆dad1	00000 00000		0 0 0 0 0	3 7
∆dad2	<b>()</b> () () () () () () () () () () () () ()	<ul> <li>3</li> <li>3</li> <li>4</li> <li>5</li> <li>5</li> <li>6</li> <li>6</li> <li>7</li> </ul>	0 © 20 5	3 7
∆dad3	<ul> <li>3</li> <li>3</li> <li>3</li> <li>3</li> <li>4</li> <li>5</li> <li>6</li> <li>6</li></ul>	© © © <sup>  </sup> © © © <del>  </del>	000 0000	3 7
∆dad5	<ul> <li>(a)</li> <li>(b)</li> <li>(c)</li> <li(c)< li=""> <li(c)< li=""> <li(c)< li=""> <li>(c)</li></li(c)<></li(c)<></li(c)<></ul>			3 7
∆dph2			0007	3 7
∆dps1		0000 0000	000	3 7
Δduo1	0092 0092	0 1 1 1 1 8 2 2 1 1		3 7

Thiabendazol (µg/m	le I) 0	8	10	Day
∆erd2	•••* •••*	• • • . • • • • .	୍ ର ର ୁ କାର୍କ ଜାନ୍ତ୍ର	3 7
∆est1	0 0 4 0 0 4		<b>6</b> 633	3 7
∆gcn5	003&	<b>0</b> 007	●◎ ◎ ● ◎ ③ *	3 7
∆git1	00 <i>%</i> *	©	©	3 7
∆git5	0003 0003	<b>0</b> 000	●● ● ●	3 7
∆iec1		• • • • • •	000 000 *	3 7
∆iec3	0004	<b>.</b>	(000 k	3 7
∆ies2	0033 0033	000** 000**	<ul> <li>•</li> <li>•</li></ul>	3 7
∆ies4				3 7
∆ies6			- ● ÷ ● ÷ ÷ = =	3 7
∆lcf1	() () () () () () () () () () () () () (	888 884	• : : : • •	3 7
∆mcl1	<ul> <li>● ⇒</li> <li>● ⇒ ÷ ∴</li> </ul>	1000 - 1000 1000 - 1000		3 7
∆mfm2			● ● ● ↓ ● ● ● ⇒ ⇒	3 7
∆mhf1	● ③ ☆ → ● ◎ ☆ →	\$\$\$` \$\$\$\$\$	(1) (1) (1) (1) (1) (1) (1) (1) (1) (1)	3 7
∆mhf2			ම ල ම ් ම ල ෯ නී	3 7
∆mms1	<b>.</b>			3 7
∆mug166	•••**	0000 00000	000i	3 7
∆ngg1	* 600	•••• ••••	.●⊗⊚ <sup>©</sup> ●⊛⊛ <sup>®</sup>	3 7
Δnht1	0000	0000	0000	3 7

Thiabendazole (µg/ml)	0	8	10	Day
Δηρρ106	• • • • • •	<b>.</b> 	•• •••	3 7
Δnrm1	<b>.</b> 	©	● @ & &	3 7
Δphp3		●● <sup>●</sup> ●● <sup>●</sup> <sup>●</sup> <sup>●</sup>	●● <i>●</i> ●● <i>●●</i>	3 7
Δpmd1	<b></b> <b></b>	<b>0</b> 00% <b>0</b> 0%	<b>6</b> 665*	3 7
∆ppr1	00\$\$	<b>.</b>	••• ••• •••	3 7
∆rad24	<ul> <li>•     </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•       </li> <li>•      </li> <li>•       </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•      </li> <li>•       </li> <li>•      </li> <li>•       </li> <li>•       </li> <li>•      </li> <li>•       </li> <li>•       </li> <lp>•      </lp></li> <lp>•     <!--</th--><th></th><th><ul> <li></li> <li><th>3 7</th></li></ul></th></lp></li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></ul>		<ul> <li></li> <li><th>3 7</th></li></ul>	3 7
∆rad32	<ul> <li>● ● </li> <li>● ● </li> </ul>	©©` ©©&&:	● ●● 终 :	3 7
∆rav1	•••**		••* ••*	3 7
Δrhp51	• • • • • • • • • • • • • • • • • • •	। सिंह की कि सिंह की कि	୍ଷ (କାର୍ଶ୍ୱ କାର୍ଚ୍ଚ	3 7
∆rhp54	@@ @@	● © ● @ ♡ ,	0 0 5 1	3 7
∆rhp55				3 7
∆rpa12	00000 0000	0000 0000 0000	003 003	3 7
∆rrd1	000×	5 9 9 9 6 9 9 9	006 0069	3 7
∆rsc1	000 <sup>0</sup>	••• •••	© © ⊙ © © ⊕ ⇔	3 7
∆rsc4	<ul> <li>•</li> <lp>• <lp>• <li>•<th><b>00</b>85 0085</th><th>ම ම ම ු ම ම ම ද</th><th>3 7</th></li></lp></lp></ul>	<b>00</b> 85 0085	ම ම ම ු ම ම ම ද	3 7
∆sce3	<b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b>	<ul> <li>(a)     <li>(b)     <li>(c)     <li>(c)</li> <li>(c)</li></li></li></li></ul>		3 7
∆SPAC17H9.08	•••*	●● <i>⊜ ⊜ ≴</i>	008÷	3 7
∆SPAC2F3.11	<b>666</b> 4		000 000₿	3 7
∆SPAC6G9.14		0000 00 % 00000 00 %		3 7

Thiabendazole (µg/ml)	0	8	10	Day
<b>∆SPAC823.10c</b>	0000 0000	0000 00000	© @ @ %	3 7
∆SPBC16H5.13	00000 00000	<ul> <li></li></ul>	000 000%	3 7
∆SPBC19G7.10c	8 13 14 8 13 14 14	6 5 T		3 7
∆spc19	•** •**	000 000 \$	6 3 3 1 1 6 8 8 4 1	3 7
∆SPCC16C4.20c		© © © . © © © .	••• ••••	3 7
<b>∆SPCC18.02</b>	<ul> <li>••••••••••••••••••••••••••••••••••••</li></ul>	0000 0000	<b>00</b> 0% 000%	3 7
∆SPCC1840.09		: ● ● @ S : ● ● @ Ø Ø	0000 0000	3 7
∆ssb3		00000 00000		3 7
∆tim11		0000 0000	●●● ◎ <sup>●</sup> ●● ● ◎ <sup>●</sup>	3 7
Δtom7	<ul> <li></li> <li></li></ul>	●●●	00 # 4 00 # 4	3 7
∆tup12	0000 0000 1000 1000	• • * * *	<b>छ</b> ® छ ५ •	3 7
Δvph2	<ul> <li></li> &lt;</ul>	* <b>* * *</b> * * * * * * * * * * * * * * *	<ul> <li>(a) (b) (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c</li></ul>	3 7
Δvps35		· (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)	<b>0</b> 03) 10003	3 7
∆vps901		<b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b>	0000 0000	3 7
∆yaf9	<ul> <li>•     </li> </li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></li></ul>	<b>.</b>	<ul> <li></li> <li><th>3 7</th></li></ul>	3 7
Δyox1	<ul> <li>● ※ *</li> <li>● ※ *</li> </ul>	/●● & ? /●● & ?	ି <b>କ</b> ିଲ୍ଲ ୍ରି : ତ କିଲ୍ଲ ଥିଲ	3 7

Cisplatin (mM)	0	1.2	1.6	Day	Cisplatin (mM)	0	1.2	1.6	Da
WT	● ● ◎ ◎ ◎ / ● ● ● Ø /9/	•••• ••••	• 0 / • • • • •	3 7	∆coq2	0005 0005	• • • • •	• • • •	3 7
nda3	••**/ ••**/	••••] ••••]	• • • •	3 7	∆coq3	© © © © ? • • • • • *	• • • • •	••••	3 7
∆abo1			••• ••••	3 7	∆coq4	••***	00 × 3	• • • •	3 7
∆ada1	` <b>€</b>	ि © © © ः () <b>© © ©</b> () ()	() () () () () () () () () () () () () () () () () (	3 7	∆coq6	00 2 15 00 2 15		• • • • •	3 7
∆ada2		<ul> <li>9</li> <li>9</li> <li>9</li> <li>9</li> <li>9</li> </ul>		3 7	Δcoq7		0001	0000N	3 7
∆apl5			• • • • *	3 7	∆cor1		0000	••••	3 7
∆apl6	688 688	€ 8 3 *	0 0 2 F	3 7	Δcox19	0083 0083	• • • • •		3 7
∆arp42	<b>0</b> 007	• • • • • •	• @\@ + • • • • •	3 7	∆cox6	<ul> <li>●</li> <li>●</li></ul>	000 ±		3 7
∆arp5	● @ 등 :) ● <b>@</b> 등 4	• • • • •		3 7	∆cph2	0000 0000 0000	0003 0003	• • • • •	3 7
∆arp8	0 9 8 % 0 9 8 %	•••**	••• ••••	3 7	∆csn1	68 68	:●@@`` ●@@```	• • • • •	3 7
∆ase1	00999 00999	•••• ••••		3 7	∆csn2	●●●*** ●● <b>●</b> ***		000 000	3 7
∆atd1	<b>6 8</b> % 4	• • • • •	• 8 C 1 • 8 6 5	3 7	∆ctp1	<ul> <li>S</li> <li>S</li> <li>S</li> </ul>	• • • • • •	<ul> <li>Ø</li> <li>Ø</li> <li>Ø</li> <li>Ø</li> <li>Ø</li> <li>Ø</li> </ul>	3 7
∆caf1	●● ∰ ∰ • ●● ∰ ∰ <b>*</b>	• • • 3	• • • •	3 7	∆dad1	003****	••• •••	• • · · · · · · · · · · · · · · · · · ·	3 7
∆cay1			0.0 · · · · · · · · · · · · · · · · · ·	3 7	∆dad2	> <b>●</b> ●●= ●●===============================			3 7
∆cbp6	0000	• • • • •	0 0 0 °	3 7	∆dad3	<ul> <li>(a) (b) (b) (b) (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c</li></ul>	0 <sub>0</sub> 0× 0 <sub>0</sub> 0≄	•••	3 7
∆ccr4	000% 000%		000 000 000	3 7	∆dad5	<b>.</b>		000 0 0 000 0	3 7
∆cdt2	<b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b> <b>.</b>		•••	3 7	∆dph2			0000 0008	3 7
∆clr5	<b>699</b> 0 6998	© © © 3 © © © 3	000 000 9	3 7	∆dps1	6 @ @ @  #}	••••		3
Δcoq10		• • • • •	• • * * • • * *	3 7	∆duo1				3 7

Day

Cisplatin (mM)	0	1.2	1.6	Day	Cisplatin (mM)	0	1.2	1.6	Day
∆erd2			• •	3 7	Δnpp106	● (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)		005 · · · · · · · · · · · · · · · · · ·	3 7
∆est1	Osta Osta	<ul> <li>0</li> <li>0</li></ul>	00 00	3 7	Δnrm1		• • • •	• • • •	3 7
∆gcn5	00000 00000	000 000	● © _ ● © @ *	3 7	∆php3	0080 0080	<ul> <li>• • • • •</li> <li>• • • • • •</li> </ul>	000 P	3 7
∆git1			• • • • •	3 7	∆pmd1	000 % 000 %	0000 000 000 000	• ø ø ø • • • • •	3 7
∆git5				3 7	Δppr1	0000 0000		• • • s	3 7
Δiec1	00000 00000		• • • •	3 7	∆rad24	0 8 9 0 0 8 9 0	••• /••••	• • •	3 7
Δiec3	0000 0000 0000 0000 0000	• • • • •		3 7	∆rad32	●● ③ <sup>③</sup> ●● ③ <sup>③</sup>	••• ••••	<b>ତ</b> ୍ତ୍ କ୍ କ	3 7
Δies2	<b>0</b> 0%%	••••	•••	3 7	∆rav1	) کے چھ یہ ا	9 9		3 7
Δies4		••••		3 7	∆rhp51	<ul> <li></li></ul>	00 k /		3 7
Δies6		O D THE	® ⊕ . ● @ = ≤	3 7	∆rhp54	<b>.</b> 	●◎ ; ●◎ ⊕ ⊕	0 0 4 0 0 4 7	3 7
Δlcf1	005° 005*	••••••••••••••••••••••••••••••••••••••	0 0 <sup>0</sup>	3 7	∆rhp55		● Ø <sup>3</sup> ; ● Ø <sup>3</sup> 3 ;	• • • *	3 7
Δmcl1	<ul> <li>Image: Second sec</li></ul>		• • • •	3 7	Δrpa12			••	3 7
∆mfm2	張 參 《 (		•• • •	3 7	∆rrd1	<ul><li>● ● ● ⊕ ⊕</li><li>● ● ● ⊕ ⊕</li></ul>	9993 9993	••••	3 7
Δmhf1			• • • •	3 7	∆rsc1			• • • • »	3 7
Δmhf2		• • • •	• • • • •	3 7	∆rsc4		•••••		3 7
∆mms1	() () () () () () () () () () () () () (		<ul><li>• • • • •</li></ul>	3 7	∆sce3	960 9 <b>6</b> 0	000×	#200 . ●200	3 7
Δmug166	<b>.</b>	<ul> <li>● ● ● </li> <li>● ● ● </li> </ul>	•••*	3 7	<b>∆SPAC17H9.08</b>	<ul> <li></li> <li><td>000 v</td><td>•••••</td><td>3 7</td></li></ul>	000 v	•••••	3 7
Δngg1	<u>୦୦୬</u> ର୍ ୦୦୬ର୍	© © © © ©	••• ••••	3 7	∆SPAC2F3.11	0000 100000 1000000	• c = #	<ul> <li>0</li> <li>0</li> <li>0</li> <li>0</li> <li>0</li> </ul>	3 7
Δnht1	000 #		000 0000	3 7	∆SPAC6G9.14	(0000 (0000	<ul> <li>●● ◎ ◎ ⇒</li> <li>●● ◎ ◎ ⇒</li> </ul>	•••• ••••	3 7

Cisplatin (mM)	0	1.2	1.6	Day
<b>∆SPAC823.10</b> c	<b>●●</b> 物 後 ●●物 後	•••; •••;	0 0	3 7
∆SPBC16H5.13	0 0 0 0 0 0 0 0 0		•	3 7
∆SPBC19G7.10c	06- 06-7	<b>ର ଓ ଓ</b> ୯	●	3 7
∆spc19	<ul> <li>\$\$\$</li> <li>\$\$\$</li> </ul>	• • • •	• • • • •	3 7
∆SPCC16C4.20c	0000 0000	<b>90</b> 0 -	000 0002	3 7
ΔSPCC18.02			••••*	3 7
∆SPCC1840.09		•••• •••	• • • • · · · · · · · · · · · · · · · ·	3 7
∆ssb3	●●@ <i>₫</i> ●●@ <i>₫</i>	••• •••		3 7
∆tim11	/●●●卷 ●●● <b>●</b> 卷	• • • • •	• • • • •	3 7
Δtom7		000) 0000	•••••	3 7
Δtup12	<ul> <li>● ● 章 →</li> <li>● ● 章 ◆ →</li> </ul>	• • • • *	••••	3 7
Δvph2	0 00 %	000 000		3 7
Δvps35	(Ö)) (Ö) () (Ö) (Ö) (Ö) (Ö) (Ö) (Ö) (Ö) (Ö) (Ö) (	•••	(• • (• • /.	3 7
Δvps901			● = ● ● 15	3 7
∆yaf9	<b>\$\$\$</b> \$	●_@ d = : ● @ d = ?	000 0000	3 7
Δуοχ1		/••• /•••		3 7



Saha (mM)	0	10	Day
∆coq2	<b>0</b> 8 8 8 <b>0</b> 8 8 8	●●法 × ●●法 本	3 7
∆coq3	- ● <u>●</u>	06%	3 7
∆coq4	••••••••••••••••••••••••••••••••••••••	0095 0095 5	3 7
Δcoq6	<b>. 9</b> 9 9 5 <b>.</b> 9 9 9 5	<ul> <li></li> <li><!--</th--><th>3 7</th></li></ul>	3 7
Δcoq7	<b>. 68</b> 83 1. <b>68</b> 83 1.		3 7
∆cor1	00.21	000% **	3 7
∆cox19	<u>*</u> @@@ *	<ul> <li>●● 金东</li> <li>●● 金东</li> </ul>	3 7
Δсох6	••**	● <sup>●</sup> <sup>●</sup> <sup>●</sup> <sup>●</sup>	3 7
∆cph2	0 & % 0 & % 1	<b>.</b>	3 7
∆csn1	0000 0000	0 6 s	3 7
∆csn2		/0 %	3 7
∆ctp1	<b>.</b> (8) (8) (8) (8) (8) (8) (8) (8) (8) (8)	●\$ ●\$\$ ●\$	3 7
∆dad1	<ul> <li>● ● 例 ※</li> <li>● ● 例 ※</li> </ul>	●● <sup>(</sup> * * * * * * * * * * * * * * * * * * *	3 7
∆dad2	() () () () () () () () () () () () () (	<ul> <li>(2) (2) (3)</li> <li>(2) (2) (3)</li> <li>(2) (2) (3)</li> <li>(3) (3) (3)</li> <li< th=""><th>3 7</th></li<></ul>	3 7
∆dad3	<b>00</b> 88 <b>00</b> 88	<b>.</b>	3 7
∆dad5	/●@@ > ●@∰ >	<b>6 8 2 1</b>	3 7
∆dph2	• • • • * / / • • • • * /	0024 0024	3 7
∆dps1		•••**	3 7
∆duo1	() () () () () () () () () () () () () (	<ul> <li>응 원 전</li> <li>응 원 전</li> </ul>	3 7

Saha (mM)	0	10	Day
∆erd2	` <b>●</b> ● * ●● *	@@ @@	3 7
Δest1	0890 0890	885 885	3 7
∆gcn5	• • • • • • • • • • • • • • • • • • •	<ul> <li>(2)</li> <li>(3)</li> <li>(3)</li> <li>(3)</li> <li>(4)</li> <li>(5)</li> <li>(6)</li> <li>(6)</li></ul>	3 7
∆git1	00 00 00 00 00	() () 등 : () () 등 () () () () () () () () () () () () ()	3 7
∆git5	© 8 % ``	() () () () () () () () () () () () () (	3 7
∆iec1	<b>●</b> ●●● ●●●●	<b>6</b> 0000	3 7
∆iec3	000¥		3 7
∆ies2	0003 0003		3 7
∆ies4		• • • • • •	3 7
∆ies6	•• ••	00 S	3 7
∆lcf1	😂 💩 🎄 🗠 🚭 🎒 🆓 🗠	े क्ष <b>क्ष</b> ने क्ष <b>क्षि</b>	3 7
Δmcl1	، و 9 و • ف 9 و و	<b>. O</b> () () () () () () () () () () () () ()	3 7
Δmfm2	00 <sup>9</sup> 3 00 <sup>9</sup> 3	000 () 000 ()	3 7
∆mhf1		<ul> <li>Ø</li> <li>Ø</li> <li>Ø</li> <li>Ø</li> </ul>	3 7
Δmhf2	●●● # A. ●●● # A.	● ● ₽ = ● ● ₽ # =	3 7
Δmms1	8 8 3 3 3 8 8 8 3	<ul> <li>3</li> <li>3</li> <li>4</li> <li>4</li> <li>5</li> <li>6</li> <li>6</li> <li>7</li> <li>7</li> <li>8</li> <li>8</li> <li>7</li> <li>9</li> <li>9</li></ul>	3 7
Δmug166	<b></b>		3 7
∆ngg1	는 은 영 영 😋 당 🏵 🕲 💿	<b>000</b> 000	3 7
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∆rhp55		<ul> <li>(2)</li> <li>(3)</li> <li>(4)</li> <li>(5)</li> <li>(4)</li> <li>(5)</li> <li>(5)</li> <li>(6)</li> <li>(7)</li> <li>(7)</li></ul>	3 7
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#### **Supplementary Materials and Methods**

#### Chemical Synthesis of SAHA

Unless stated otherwise, all non-aqueous reactions were performed in dried, round-bottomed flasks under an inert nitrogen atmosphere. Commercially available, AR-grade dichloromethane (DCM) and methanol (MeOH) were used as received. All reaction temperatures stated in the procedures are external bath temperatures. Commercial reagents were purchased from Sigma-Aldrich or Alfa Aesar, and used as received without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise stated. Reaction progress was monitored by analytical thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60F-254) used UV light (254 nm) for visualization, and ceric ammonium molybdate or potassium permanganate solutions as developing stains. Flash chromatography was performed on silica gel 60 (0.040 - 0.063 mm) purchased from SiliCycle or Merck. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker AMX400 (400 MHz) NMR spectrometer at ambient atmosphere. The deuterated solvent used was CDCl<sub>3</sub> unless otherwise stated. Chemical shifts are reported in parts per million (ppm), and residual undeuterated solvent peaks were used as internal references: proton (7.26 ppm for CDCl<sub>3</sub>, 2.50 ppm for DMSO-d6), carbon (77.0 ppm for CDCl<sub>3</sub>, 39.52 ppm for DMSO-d6). <sup>1</sup>H NMR coupling constants (J) are reported in Hertz (Hz), and multiplicities are presented as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), and br (broad). Low resolution mass spectra were obtained on an Agilent 6130B Quadrupole LC/MS in ESI mode.

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1.5 ml (8.53 mmol) of monomethyl suberate was dissolved in 30 ml of DCM and cooled to 0°C. 1.2 ml (10.9 mmol, 1.3eq.) of N-methylmorpholine and 1.0 ml (10.5 mmol, 1.2eq.) of ethyl chloroformate was added to the solution at 0°C and stirred for 15 min at 0°C. 1.0 ml (11.0mmol, 1.3eq.) of aniline was added at 0°C and the solution was allowed to warm to room temperature over 18 h. The reaction was quenched by the addition of saturated sodium bicarbonate to the solution. The mixture was extracted with DCM 3 times. The combined organic layer was washed with brine solution and dried with anhydrous sodium sulfate. The organic layer was concentrated and purified by column chromatography using 4:1 to 3:2 to 1:1 Hex/EtOAc to obtain 2.00 g (89%) of the amide as a brown solid. TLC (3:2 Hex/EtOAc)  $R_f = 0.31$ ; ESI M+1 263.2

<sup>1</sup>H NMR 8.23 (br. s., 1 H), 7.54 (d, *J* = 7.8 Hz, 2 H), 7.27 (t, *J* = 7.8 Hz, 2 H), 7.09 - 7.03 (m, 1 H), 3.65 (s, 3 H), 2.31 (td, *J* = 7.5, 17.1 Hz, 4 H), 1.74 - 1.64 (m, 2 H), 1.60 (quin, *J* = 7.3 Hz, 2 H), 1.37 - 1.28 (m, 4 H).

<sup>13</sup>C NMR 174.2, 171.8, 138.1, 128.7, 123.9, 119.9, 51.3, 37.2, 33.8, 28.6, 28.6, 25.3, 24.5.

2.00 g (7.61 mmol) of amide **A1** was dissolved in 20 ml of methanol and cooled to 0°C. 2.68 g (38.5 mmol, 5.1eq.) of hydroxylamine hydrochloride salt and 15.0 ml (78.7 mmol, 10.3eq.) of 30% sodium methoxide solution in methanol was added to the solution. The reaction mixture was stirred for 2 h at 0°C was and then quenched with 20 ml of 4 M hydrochloric acid. The mixture was concentrated to remove methanol. The resultant precipitate was

filtered and recrystallized from methanol and water to obtain 1.66 g (82%, 74% over 2 steps) of SAHA, **1**, as an off-white crystalline solid. ESI M+1 265.2

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 10.32 (br. s., 1 H), 9.83 (s, 1 H), 8.65 (br. s., 1 H), 7.58 (d, *J* = 7.5 Hz, 2

H), 7.33 - 7.23 (m, 2 H), 7.06 - 6.97 (m, 1 H), 2.28 (t, *J* = 7.5 Hz, 2 H), 1.94 (t, *J* = 7.4 Hz, 2

H), 1.64 - 1.43 (m, 4 H), 1.35 - 1.20 (m, 4 H).

 $^{13}$ C NMR (DMSO-d<sub>6</sub>)  $\delta$  = 171.2, 169.1, 139.3, 128.6, 122.9, 119.0, 36.4, 32.2, 28.4, 25.0.