

Table 3. Genetic alterations conferring hypersensitivity to Top1 poisoning in budding yeast:

<b>Yeast <i>Saccharomyces Cerevisiae</i></b>				<b>Humans</b>		
<b>Gene</b>	<b>Effect</b>	<b>Refs.</b>	<b>Function</b>	<b>Gene</b>	<b>Effect</b>	<b>Refs.</b>
<b><i>RAD52/51</i> homologous recombination (HR)</b>						
RAD52	HS	(8, 98, 99, 131, 235-237)	Strand annealing	RAD52	?	
RAD51	HS	(98, 99, 131, 236)	RecA homolog: strand invasion	RAD51C	HS	(223)
RAD55	HS	(98, 99, 131)	Strand annealing, exchange	XRCC2	HS	(219, 234), 230,
RAD57	HS	(98, 99, 131)	Strand annealing, exchange	XRCC3	HS	(219)
RAD54	HS	(98, 99)	ATPase			
MMS1	S	(99, 238)	Replication repair/epistatic Rad52			
RAD59	S	(98, 99)	Rad52-related recombination			
<b><i>MRX (MRN) 3'-nuclease/checkpoint (HR + NHEJ)</i></b>						
SAE2	HS	(99)	Activates Mre11 endonuclease; meiotic and mitotic recombination			
MRE11	HS	(97-99, 237)	MRX/N complex; endonuclease	MRE11	?	
RAD50	HS	(99, 131, 236)	MRX/N complex; scaffold	RAD50	?	
XRS2	HS	(131)	MRX/N complex; signaling	NBS1	HS	(212, 221)
<b><i>Mus81/Mms4 (Mus81/Eme1) 3'-Flap Endonuclease</i></b>						
MUS81	S	(98, 99, 126, 131)	3'-flap endonuclease with Mms4	MUS81	NS	(137)
MMS4	S	(98, 99, 126)	Partner for Mus81 endonuclease	EME1	?	
<b><i>Tdp1-PNKP 3'-end processing</i></b>						
TDP1	CS [b]	(97-99)	Tyrosyl-DNA phosphodiesterase	TDP1	?	(93, 94, 224)
TPP1	CS [b,c]	(98, 110)	Polynucleotide 3'-phosphatase	PNKP [b]	HS	(115)
APN1	CS [b,c]	(97, 98, 236)	AP endonuclease (endo IV family)			
APN2	CS [b,c]	(97, 98)	AP endonuclease (exo III family)	APE1	?	
<b><i>Rad1/Rad10 (XPF/ERCC1) 3'-endonuclease</i></b>						
RAD1	CS [b]	(97-99, 236)	3'-flap endonuclease with Rad10	XPF	NS	(our observations)
RAD10	CS [b]	(97, 98)	Partner for Rad1	ERCC1	NS	
<b><i>Rad27 (FEN1) 5'-endonuclease</i></b>						
RAD27	MS	(98, 99, 133)	5'-flap endonuclease	FEN1	HS	(133)
SLX4/SLX1	MS	(99)	Endonuclease with broad range of activities against various substrates	?		
<b><i>Mismatch repair</i></b>						
MMS1	S	(99)	Mismatch repair			
<b><i>RecQ/Top3 helicases/topoisomerase</i></b>						
SGS1	MS	(126, 131)	Top3-associated helicase	WRN; BLM	HS	(82, 227-229)
SRS2	S	(98, 99)	Rad51-associated helicase		?	
TOP3	S	(98, 126)	Replication/recombination topoisomerase	TOP3 $\alpha$ TOP3 $\beta$	?	
<b><i>9-1-1 ("PCNA-like") Clamp</i></b>						
DDC1	MS	(98)	Replication/Repair Clamp; "9-1-1"	RAD9	?	
RAD17	MS	(131, 236, 239)	Replication/Repair Clamp; "9-1-1"	RAD1	?	
MEC3	MS	(131)	Replication/Repair Clamp; "9-1-1"	HUS1	?	
RAD24	MS	(237)	Clamp loader for 9-1-1	RAD17	?	

(Table 3: Continued from previous page)

<b>Budding Yeast (YSC)</b>				<b>Humans</b>		
<b>Gene</b>	<b>Effect</b>	<b>Refs.</b>	<b>Function</b>	<b>Gene</b>	<b>Effect</b>	<b>Refs.</b>
<b>Replication</b>						
CDC45	S	(134)	Initiation of DNA replication	CDC45L	?	
POL32	MS	(131)	Small subunit for Pol $\delta$	TEX14	?	
TRF4	S	(240)	DNA polymerase	POLS	?	
DPB11	S	(134)	Replication initiation/checkpoint	TOPBP1	?	
RAD6	MS	(131, 236, 241)	PRR [d]; Ub conjug	RAD6A, B	?	
RAD18	S	(131, 236)	PRR [d]; loads Rad6	RAD18	?	
SLX4	MS	(99)	DNA replication	?		
CLB5	S	(99)	B type cyclin	Cyclin B	?	
Dcc1	S	(242)	Sister chromatid cohesion	?		
<b>Transcription</b>						
HPR1	S	(131)	Transcription & recombination	MGC5350	?	
SFP1	S	(131)	Transcription factor	REQ	?	
CCR4	S	(131)	Transcription	KIAA1194	?	
BUR2	S	(131)	Cyclin partner for Bur1	Cyclin H	?	
RPB9	S	(131)	RNA polymerase subunit	POLR21	?	
HTZ1	S	(99)	Regulation of transcription from Pol II promoter			
SPT21	S	(99)	Regulation of transcription from Pol II promoter			
PAT1	S	(99)	Controls mRNA decay			
LSM1	S	(99)	Controls mRNA decay			
HMO1	S	(99)	Involved in rDNA transcription			
MPH1	MS	(131, 241)	RNA helicase	MPH1	?	
<b>Sensor PI3K-related protein kinases</b>						
MEC1	HS	(236, 237)	PI3LK checkpoint sensor kinase	ATR	HS	(163)
DDC2	?		Partner for MEC1	ATRIP	?	
TEL1	S	(237)	PI3LK checkpoint sensor kinase	ATM	HS	(211-214)
			PI3LK checkpoint sensor kinase	DNA-PK	HS	(56, 219)
<b>Transducer protein kinases; BRCT proteins</b>						
RAD53	MS	(236)	Checkpoint effector kinase	CHK2	S	(162, 218)
RAD9	MS	(236, 237)	Adaptor for checkpoint kinases	MDC1	?	
				BRCA1	HS	(216)
<b>Chromatin</b>						
HTA1/2	S	(237)	Histone H2A	H2AX	S	(53)
HHF1/2	S	(243)	Histone H4	H4	?	
GCN5	S	(244)	Histone H3 acetyltransferase	PCAF	?	
YNG2	S	(244)	Histone H4 acetyltransferase	ING1-5	?	
ESA1	S	(243)	Histone H4 acetyltransferase	MYST1/HAT	?	
ASF1	S	(98)	Chromatin assembly	ASF1B	?	
MCD1	S	(240)	Chromatin cohesion	RAD21	?	
CTF4	MS	(98)	Chromatid cohesion & segregation	AND-1	?	
TOF1	S	(99, 242)	Chromatid cohesion	TIM-1	?	
CSM3	S	(99, 242)	Meiotic chromosome segregation	TIPIN	?	
FUN30	S	(99)	DNA-dependent ATPase; chromosome stability			

(Table 3: Continued from previous page)

<b>Budding Yeast (YSC)</b>				<b>Humans</b>		
<b>Gene</b>	<b>Effect</b>	<b>Refs.</b>	<b>Function</b>	<b>Gene</b>	<b>Effect</b>	<b>Refs.</b>
<b><i>Ubiquitin</i></b>						
UBC9	S	(245)	Ubiquitin ligase	UBE2I	?	
DOA4	S	(245)	Ubiquitin hydrolase			
UBC4	S	(99)	Ubiquitin conjugation; stress response			
RTT101	S	(99)	Ubiquitin ligase; chromosome stability			
ULA1	S	(99)	RUB1-protein conjugation			
<b><i>Others</i></b>						
VAC14	S	(99)	Vacuole inheritance			
NUP60	S	(99)	Nucleocytoplasmic transport			
PPH3	S	(99)	Serine/threonine phosphatase			
PSY2	S	(99)	Unknown			
ILM1	S	(99)	Unknown			
CLB5	S	(99)	B type cyclin in G1/S transition			

Abbreviations for effects: HS, S, MS, and CS correspond to hypersensitivity, sensitivity, moderate sensitivity, and conditional sensitivity to camptothecin, respectively. NS: no hypersensitivity.

[a]: The Rad52 epistasis group includes the RAD 50, 51, 52, 54, 55, 57, 59, MRE11 and XRS2 genes.

[b]: Tdp1 deficiency results in HS only in the presence of Rad1/Rad10 deficiency (97, 98); conversely Rad1 deficiency does not confer hypersensitivity to CPT (126) unless the Tdp1-Apn1 pathway is defective (97). Tpp1, Apn1+Apn2+Tpp1 need to be inactivated to confer full camptothecin hypersensitivity (111); see Fig. 3A.

[c]: PNKP possesses both 3'-phosphatase and 5'-kinase activities, whereas the yeast ortholog, Tpp1 only possesses 3'-phosphatase activity. Neither Apn1, Apn2 or Tpp1 possess AP endonuclease activity (111).

[d]: PRR: post-replication repair. Deficiency of Rhp6 or Rhp18 (YSP orthologs of Rad6 and Rad18) does not confer CPT hypersensitivity (246).