

Table S1: A full list of biological reagents, chemicals, oligonucleotides and computational resources.

REAGENT	SOURCE	CATALOGUE NUMBER
Antibodies		
Rabbit polyclonal anti-53BP1 (H300)	Santa Cruz	#22760
Human polyclonal anti-Centromere protein antibody	Antibodies Inc	#15-234-0001
Goat polyclonal anti-ATM	Bethyl	#A300 135A
Mouse anti-phosphoATM (Ser1981)	Millipore	#05-740
Goat polyclonal anti-ATR	Santa Cruz	#sc-1887
Rabbit Phospho-(Ser/Thr) ATM/ATR Substrate Antibody	Cell Signalling Technology	#2851
Rabbit polyclonal anti-BLM	abcam	#ab2179
Mouse monoclonal anti-Chk1	Cell Signalling Technology	#2360
Rabbit polyclonal anti-Phospho-Chk1 (Ser345)	Cell Signalling Technology	#2431
Rabbit polyclonal anti-Chk2	Cell Signalling Technology	#2662
Rabbit polyclonal anti-Phospho-Chk2 (Thr68)	Cell Signalling Technology	#2661
Rabbit polyclonal anti-FANCD2	Novus	#NB100-182SS
Mouse monoclonal anti-GAPDH	Millipore	#MAB374
Mouse monoclonal anti- γ H2AX	Millipore	#05-636
Rabbit Polyclonal anti-Histone H3	Cell Signalling Technology	#9715
Rabbit Polyclonal anti-Hsp90	Cell Signalling Technology	#4874
Mouse monoclonal anti-Lap2	BD Biosciences	#611000
Mouse monoclonal anti-MPM2-Cy5	Millipore	#16-220
Rabbit monoclonal anti-p21	Abcam	#ab109199
Mouse monoclonal anti-p53	Santa Cruz	#sc-126
Rabbit polyclonal anti-Phospho-p53 (Ser15)	Cell Signalling Technology	#9284
Rabbit polyclonal anti-Phospho-p53 (Ser20)	Cell Signalling Technology	#9287
Mouse monoclonal anti-PCNA (PC10)	Cell Signalling Technology	#2586
Rabbit polyclonal anti-PICH	Novus	#H00054821-D01P
Mouse monoclonal anti-PML	Abcam	#ab96051
Rabbit monoclonal anti-PML-Alexa Fluor555	Abcam	#ab217524
Mouse monoclonal [9H8] to RPA32/RPA2	Abcam	#ab2175
Rabbit polyclonal anti-SMC6	Abcam	#ab18039
Mouse monoclonal anti-TRF2	Millipore	#05-521
Mouse monoclonal anti-Tubulin	Sigma	#T5168
Mouse anti-Tubulin	In-house	N/A
Rabbit anti-Caspase 3	R&D Systems	#AF835
Rabbit anti-Ki67	Abcam	#ab15580
Mouse monoclonal anti-Wip1	Santa Cruz	#sc-376257
anti-mouse Alexa Fluor488	Invitrogen	#A11001
anti-mouse Alexa Fluor555	Invitrogen	#A21422
anti-mouse Alexa Fluor647	Invitrogen	#A21235
anti-rabbit Alexa Fluor488	Invitrogen	#A11008
anti-rabbit Alexa Fluor647	Invitrogen	#A31573
anti-rabbit HRP	Cell Signalling Technology	#7074
anti-mouse HRP	Cell Signalling Technology	#7076
Chemicals		
Aphidicolin	Sigma-Aldrich	#A0781
ATM Kinase Inhibitor	Merck	#118500
ATR Kinase Inhibitor	Merck	#504972
BIM1	Sigma-Aldrich	#203290
Bleomycin	Millipore	#203401
BLU577	Kindly provided by Dr Jon Roffey, Cancer Research Technology, UK	N/A
Camptothecin	Merck	#208925

Chk1 inhibitor CCT244747	Ref (22)	N/A
Chk1 inhibitor LY2603618	APEX BIO	#A8638
Chk2 inhibitor CCT241533	Ref (23)	N/A
cOmplete™, EDTA-free Protease Inhibitor Cocktail	Roche	#4693159001
DAPI	Merck	#10236276001
EmbryoMax Nucleosides	Merck	#ES-008-D
Etoposide	Sigma	#E1383
Hydroxyurea	Sigma	H8627
ICRF193	Sigma	#I4659
Lullaby	OZ Biosciences	#LL73000
Luminata	Millipore	WBLUC0500
NuPAGE™ LDS Sample Buffer	Invitrogen	#NP0007
Nocodazole	Merck	#M1404
Phalloidin	Invitrogen	#A22283
PhosSTOP™	Roche	#4906845001
ProLong Diamond Antifade Mountant	Thermo Fisher	#P36965
Protein G Dynabeads	Invitrogen	#10004D
Propidium iodide	Sigma	#P4170
Ribonuclease A	Sigma	#R5125
RO3306	Tocris Bioscience	#4181
Oligonucleotides		
Non-targeting control pool	Dharmacon	#D-001810-10-05
siATM OTP pool	Dharmacon	#L-003201-00-0005
siATR OTP pool	Dharmacon	#L-003202-00-0005
siBLM OTP pool	Dharmacon	#L-007287-00-0005
siCDKN1A siGENOME Set of 4	Dharmacon	#MQ-003471-00-0002
siCHEK1 OTP Set of 4	Dharmacon	#LQ-003255-00-0002
siCHEK2 OTP Set of 4	Dharmacon	#LQ-003256-00-0002
siNDNL2 siGENOME Set of 4	Dharmacon	#MU-006402-00-0002
siNSMCE1 siGENOME Set of 4	Dharmacon	#MU-007157-01-002
siNSMCE2 siGENOME Set of 4	Dharmacon	#MU-018070-00-0002
siNSMCE4 OTP Set of 4	Dharmacon	#MU-017227-00-0002
siTP53 siGENOME Set of 4	Dharmacon	#MQ-003329-03-0002
siTP53 OTP Set of 4	Dharmacon	#LQ-003329-00-0002
siSMC5 siGENOME Set of 4	Dharmacon	#MU-014117-01-0002
siSMC6: GAGGGAAACGACAUAUGA	Dharmacon	#D-018408-04-0010
siTOP2A siGENOME Set of 4	Dharmacon	#MU-004239-02-0002
Organoid Culture Media and Additives		
A83-01	Sigma	SML0788-5MG
B27	Thermo Fisher	#17504044
BME	R&D Systems	#35033-010-02
DMEM/F12	Gibco	#12634010
EGF	Stem Cell Technologies	#78006.1
Gastrin	Sigma	#G9145-1mg
Glutamax	Gibco	#35053361
HEPES	In House	N/A
N-acetylcysteine	Sigma	#A7250-5G
Nicotinamide	Sigma	#72345-50G
Noggin conditioned media	In House	N/A
Pen/Strep	Gibco	#15140-122
PGE2	Tocris Bioscience	#2296
R-spondin 1 conditioned media	In House	N/A
TrypLE Express	Thermo Fisher	#12604-013
SB202190	Sigma	#57067-5MG

Y-27632	Sigma	#SCM075
Commercial Assays		
Click-iT EdU Cell Proliferation Kit, Alexa Fluor 488 dye	Thermo Fisher	#C10337
Software		
MATLAB R2017B	MathWorks	https://uk.mathworks.com/products/matlab.html
FACSDiva	BD Biosciences	http://www.bdbiosciences.com/us/instruments/research/software/flow-cytometry-acquisition/bd-facsdiva-software/m/111112/features
FlowJo V.10.1	FlowJo, LLC	https://www.flowjo.com/solutions/flowjo
Prism 8	GraphPad	https://www.graphpad.com/scientific-software/prism/
Fiji	ImageJ	https://imagej.net/Fiji