FIG. 1A

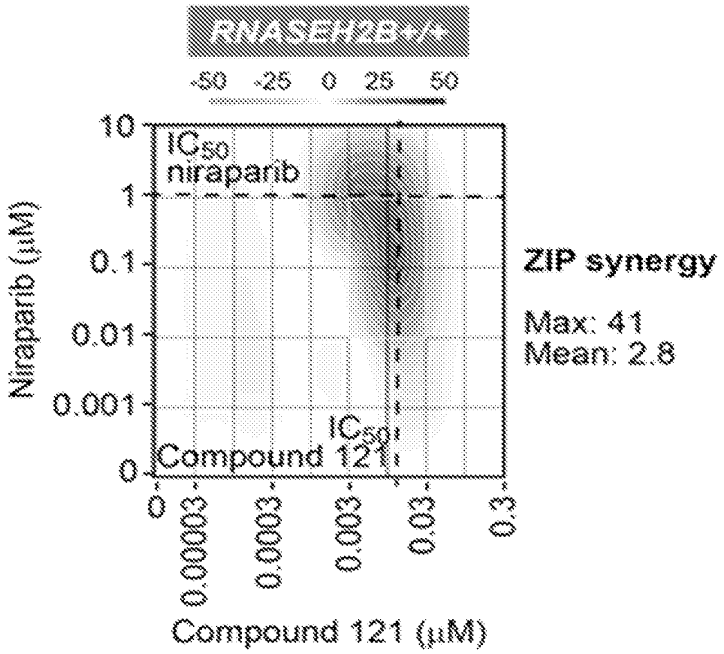

RNASEH2B+/+
-50 -25 0 25 50
10
1
0.1
0.01
0.001
0
IC50 niraparib
IC50 Compound 121
Niraparib (μM)
0 0.00003 0.0003 0.003 0.03 0.3
Compound 121 (μM)
ZIP synergy
Max: 41
Mean: 2.8

FIG. 1B

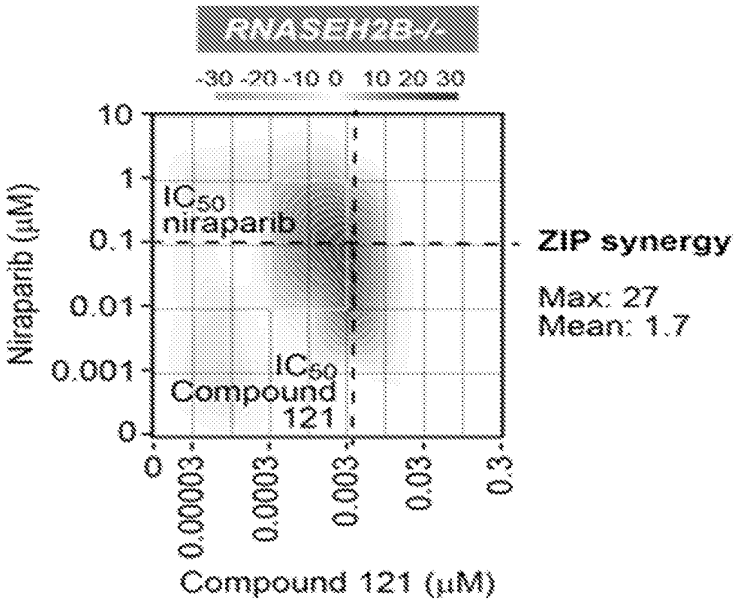
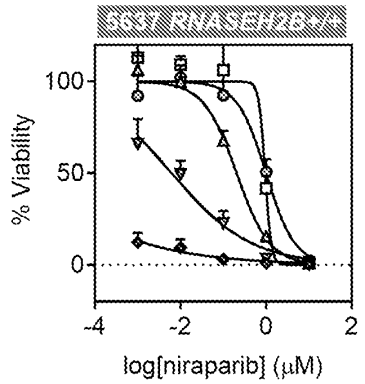
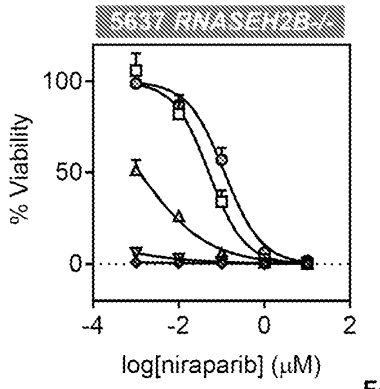

RNASEH2B-/-
-30 -20 -10 0 10 20 30
10
1
0.1
0.01
0.001
0
IC50 niraparib
IC50 Compound 121
Niraparib (μM)
0 0.00003 0.0003 0.003 0.03 0.3
Compound 121 (μM)
ZIP synergy
Max: 27
Mean: 1.7

FIG. 2A



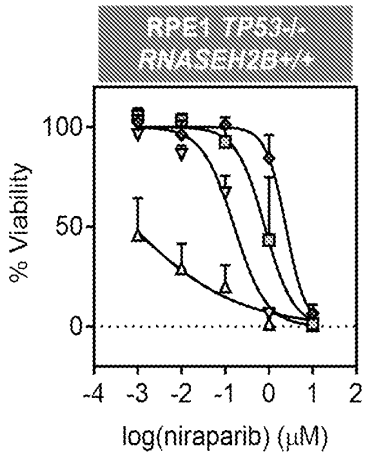
Compound 121 (ATRi) IC_{50} = 0.012 μM	Niraparib IC_{50} (μM)
DMSO	0.993
0.0012 μM	0.946
0.0037 μM	0.205
0.011 μM	0.006
0.033 μM	N/A

FIG. 2B



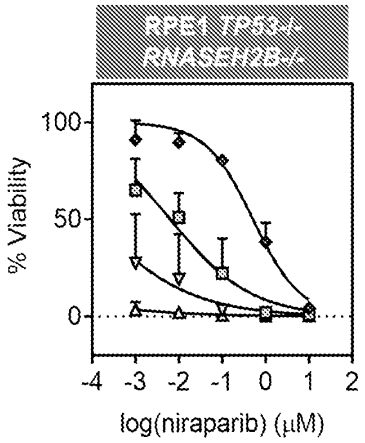
Compound 121 (ATRi) IC_{50} = 0.003 μM	Niraparib IC_{50} (μM)	Fold shift in IC_{50} from WT
DMSO	0.117	~8x
0.0012 μM	0.050	~19x
0.0037 μM	0.001	~200x
0.011 μM	N/A	
0.033 μM	N/A	

FIG. 3A



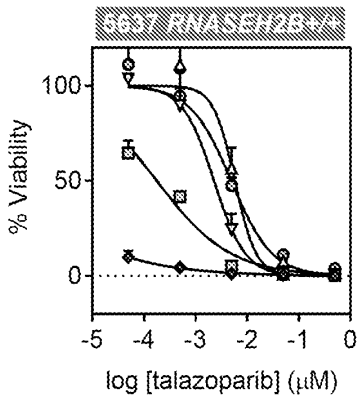
Compound 43 (ATRi) IC_{50} = 0.117 μM	Niraparib IC_{50} (μM)
DMSO	2.439
0.01 μM	0.832
0.03 μM	0.161
0.1 μM	0.001

FIG. 3B



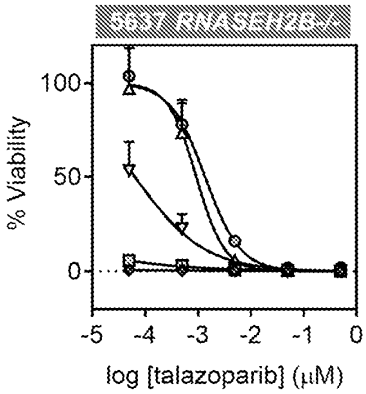
Compound 43 (ATRi) IC_{50} = 0.023 μM	Niraparib IC_{50} (μM)	Fold shift in IC_{50} from WT
DMSO	0.513	~5x
0.01 μM	0.006	~140x
0.03 μM	<0.001	>200x
0.1 μM	N/A	

FIG. 4A



Compound 121 (ATRi) IC_{50} = 0.012 μM	Talazoparib IC_{50} (μM)
DMSO	0.005
0.0012 μM	0.006
0.0037 μM	0.002
0.011 μM	0.0002
0.033 μM	N/A

FIG. 4B



Compound 121 (ATRi) IC_{50} = 0.003 μM	Talazoparib IC_{50} (μM)	Fold shift in IC_{50} from WT
DMSO	0.001	~5x
0.0012 μM	0.001	~5x
0.0037 μM	0.00006	~30x
0.011 μM	N/A	
0.033 μM	N/A	

FIG. 5A

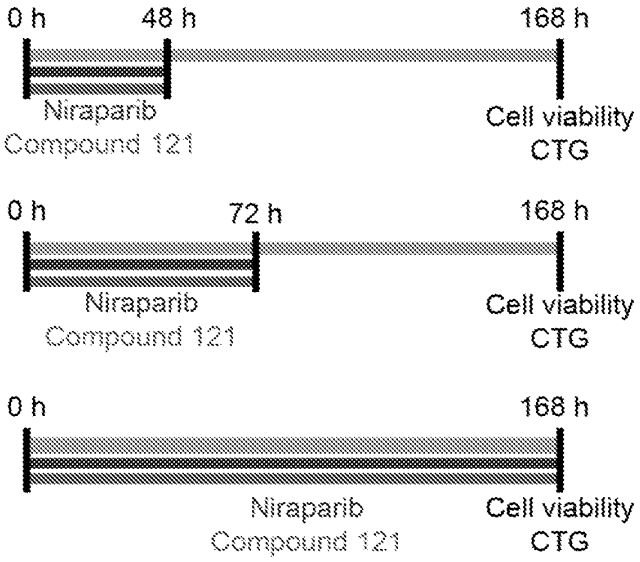

0 h
48 h
168 h
Niraparib
Compound 121
Cell viability
CTG
0 h
72 h
168 h
Niraparib
Compound 121
Cell viability
CTG
0 h
168 h
Niraparib
Compound 121
Cell viability
CTG

FIG. 5B

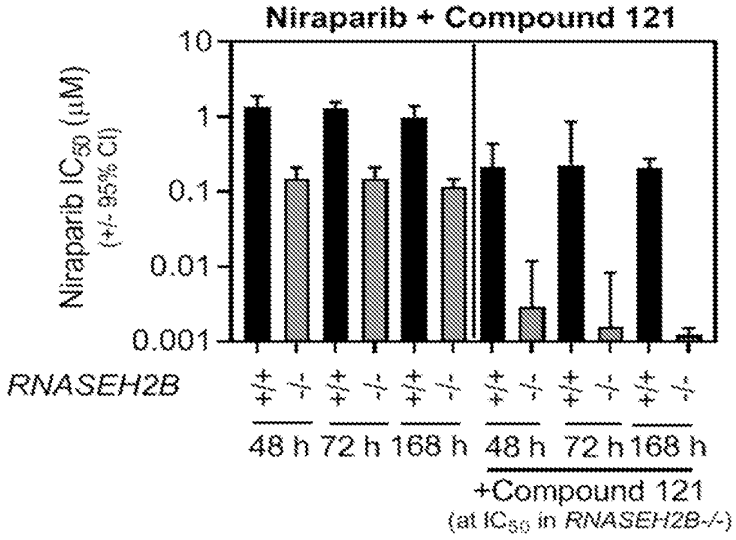
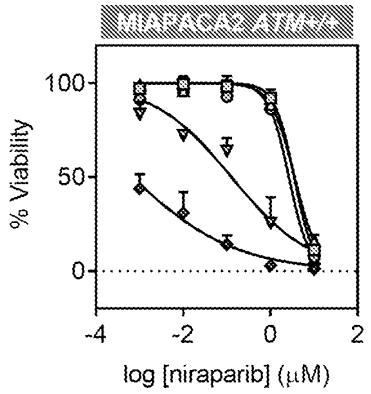
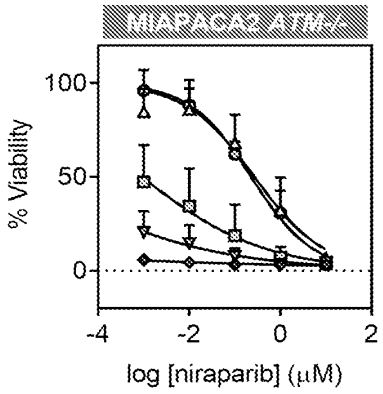

Niraparib + Compound 121
Niraparib IC50 (μM)
(+/- 95% CI)
10
1
0.1
0.01
0.001
RNASEH2B
+/+
-/-
48 h
72 h
168 h
+Compound 121
(at IC50 in RNASEH2B-/-)

FIG. 6A



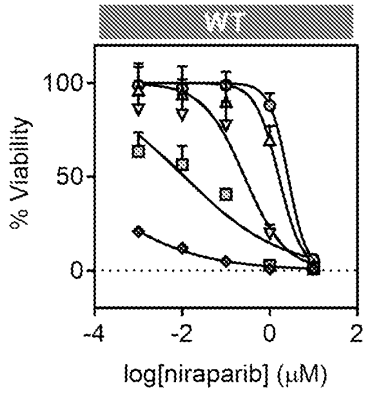
Compound 121 (ATRi) IC_{50} = 0.107 μM	Niraparib IC_{50} (μM)
DMSO	2.6
0.003 μM	3.6
0.01 μM	3.5
0.03 μM	0.128
0.1 μM	<0.0006

FIG. 6B



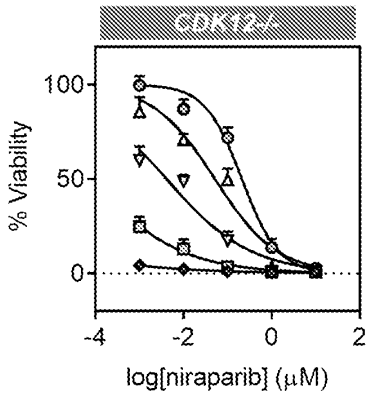
Compound 121 (ATRi) IC_{50} = 0.011 μM	Niraparib IC_{50} (μM)	Fold shift in IC_{50} from WT
DMSO	0.228	~11x
0.003 μM	0.270	~13x
0.01 μM	0.0009	~380x
0.03 μM	N/A	
0.1 μM	N/A	

FIG. 7A



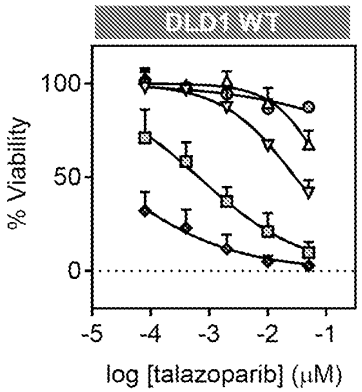
Compound 121 (ATRi) IC_{50} = 0.010 μM	Niraparib IC_{50} (μM)
DMSO	2.6
0.0012 μM	1.6
0.0037 μM	0.277
0.011 μM	0.011
0.033 μM	N/A

FIG. 7B



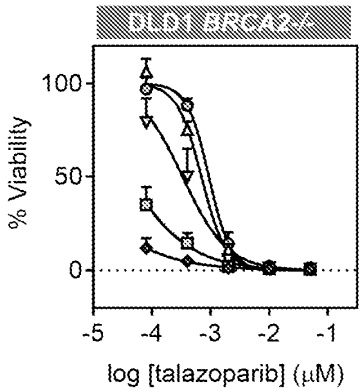
Compound 121 (ATRi) IC_{50} = 0.006 μM	Niraparib IC_{50} (μM)	Fold shift in IC_{50} from WT
DMSO	0.212	~12x
0.0012 μM	0.052	~30x
0.0037 μM	0.004	~70x
0.011 μM	~0.00007	~160x
0.033 μM	N/A	

FIG. 8A



Compound 121 (ATRi) IC_{50} = 0.061 μM	Talazoparib IC_{50} (μM)
DMSO	>0.1
0.0037 μM	~0.1
0.011 μM	0.03
0.033 μM	0.0007
0.1 μM	~0.00001

FIG. 8B



Compound 121 (ATRi) IC_{50} = 0.036 μM	Talazoparib IC_{50} (μM)	Fold shift in IC_{50} from WT
DMSO	0.0009	>100x
0.0037 μM	0.0007	>100x
0.011 μM	0.0003	100x
0.033 μM	~0.00004	~18x
0.1 μM	N/A	

FIG. 9A

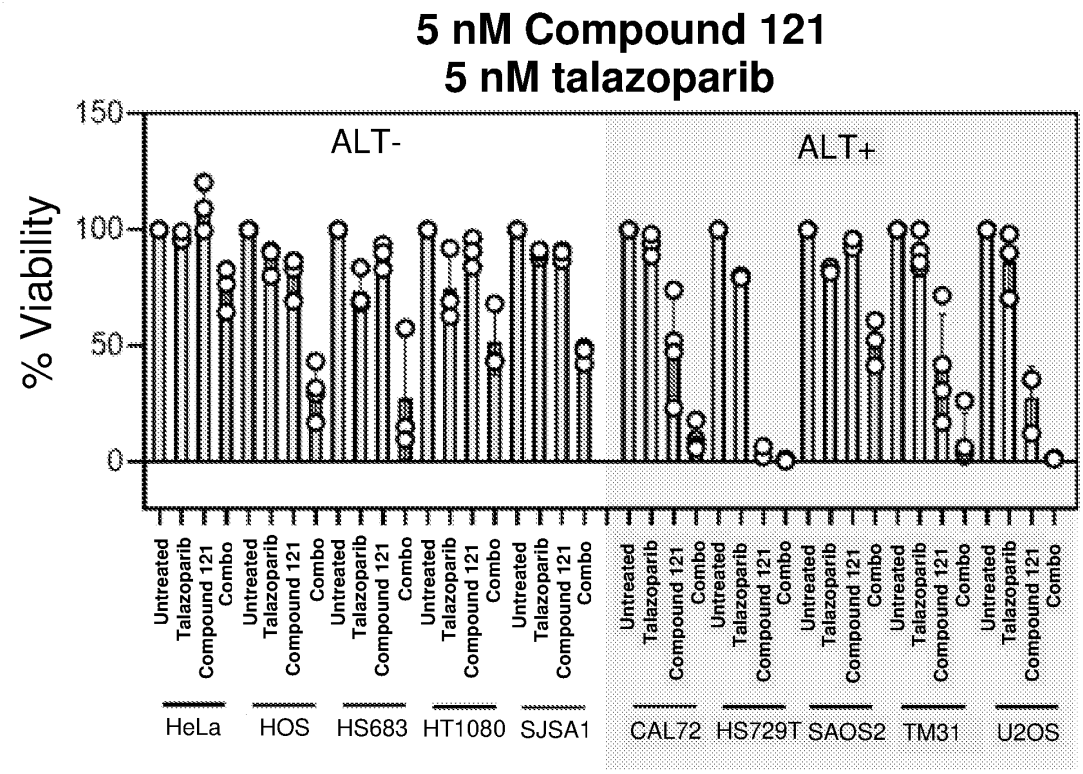
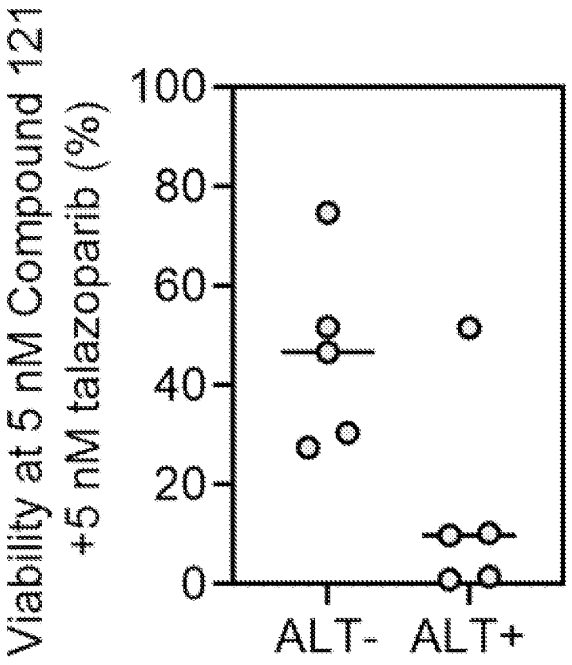

5 nM Compound 121
5 nM talazoparib
% Viability
150
100
50
0
ALT-
ALT+
Untreated
Talazoparib
Compound 121
Combo
HeLa
HOS
HS683
HT1080
SJSA1
CAL72
HS729T
SAOS2
TM31
U2OS

FIG. 9B


Viability at 5 nM Compound 121
+5 nM talazoparib (%)
100
80
60
40
20
0
ALT-
ALT+