**Supplementary Materials and Methods**

**Reagents**

Doxorubicin was purchased from LC Laboratories (Woburn, MA), Thiazolyl blue tetrazolium bromide (MTT reagent) from Alfa Aesar (Lancashire, United Kingdom), Rhodamine-123 from Sigma-Aldrich (St. Louis, MO), Crystal Violet from Fisher Scientific (Fair Lawn, NJ), DMEM High Glucose Medium (DMEM) from Hyclone/GE Healthcare Life Sciences (Pittsburgh, PA), RPMI-1640 (RPMI) from Corning Cellgro (Manassas, VA), IMDM Modified (IMDM) from Hyclone/GE Healthcare Life Sciences (Pittsburgh, PA), Fetal Bovine Serum (FBS) from Atlanta Biologicals (Flowery Branch, GA), L-Glutamine (200 mM) and PenStrep (Penicillin G 10,000 U/mL and Streptomycin 10 mg/mL) from Gemini Bio-products (West Sacramento, CA), MEM-Non essential amino acids 100x (MEM-NEAA) and Sodium Pyruvate (100 mM) from Gibco/Life Technologies (Carlsbad, CA), and Xtreme-Gene-HP transfection reagent was purchased from Roche Diagnostics (Mannheim, Germany). Zosuquidar Trihydrochloride (Zosuquidar) was obtained from the laboratory of Branimir Sikic, Stanford University.

 Antibodies used for immunoblotting were: Rabbit anti-ABCB1 (D3H1Q, 1:1000), and rabbit anti-TOP2A (D10G9, 1:1000) from Cell Signaling Technologies, Danvers, MA. Rabbit anti-SMARCB1 (A301-087A-T, 1:1000), goat anti-SMARCA4 (A303-877A-T, 1:1000), and rabbit anti-ARID1A (A301-041A-T (1:1000) from Bethyl Laboratories, Montgomery, TX. Mouse anti-αTubulin (T6199, 1:10,000) from Sigma-Aldrich, St. Louis, MO.

**Cell lines**

The Hap1 cell line ([1](#_ENREF_1)) was kindly provided by Dr.Thijn Brummelkamp, Netherlands Cancer Institute. The KOPN8 cell line was a generous gift from Professor Michael Cleary, Stanford University. The 293FT cell line used to generate high-titer lentiviruses was obtained from ThermoFisher Scientific (Grand Island, NY); the A549, PC3, MDA-MB-361, HCC-1954 and NCI-H1650 cell lines were purchased from ATCC (Manassas, VA) where they were validated by STR profiling. Cell lines were used at low passage. The Phoenix-Ampho cell line used for retrovirus production was purchased from Allele Biotechnology (San Diego, CA). The SNU-349 cell line was obtained from Korean Cell Line Bank.

 Hap1 cells were grown in IMDM with 10% FBS and 2mM L-Glutamine; 293FT, Phoenix-Ampho and MDA-MB-361 cells in DMEM with 10% FBS, 1 mM Sodium Pyruvate, 1x MEM-NEAA and 2 mM L-Glutamine; A549, PC3, HCC-1954, NCI-H1650 and KOPN8 cells in RPMI with 10% FBS and 2mM L-Glutamine. Unless stated otherwise, PenStrep was added to all media at final concentration of 60 U/mL for Penicillin-G and 60 µg/mL for Streptomycin.

**Haploid genetic screen**

Generation of mutagenized cells was accomplished as described previously ([2](#_ENREF_2)), with some modifications. Gene-trap (GT) retrovirus was produced in 293FT cells. A total of 9x107 cells were seeded in 6 T-175 flasks in DMEM growth media without antibiotics 24 hrs before transfection. Cells in each T-175 flask were transfected with 6.6 μg of an equimolar mixture of pGT-GFP, pGT-GFP+1 and pGT-GFP+2 (diagrammed in Supplementary Figure 1A)([3](#_ENREF_3)) combined with 1.7 μg pAdvantage (Promega, Madison, WI), 2.6 μg pCMV-VSV-G and 4 μg pCMV-Gag-Pol (both from Cell Biolabs, San Diego, CA) using 45 μl of X-tremeGENE HP transfection reagent. The media was refreshed ~20 hrs post-transfection, and retrovirus-containing supernatant was collected ~46 hrs and ~54 hrs post-transfection. The virus-containing supernatant was immediately filtered through 0.45 μm Acrodisc low protein binding syringe filters (Pall, Fribourg, Switzerland) and concentrated by ultracentrifugation for 1.5 hr at 23,000 rpm in a Sorvall Surespin 630 rotor. Most of the supernatant was removed, leaving behind ~1 ml to cover the pellet, the virus was incubated at 4°C for ~12 hrs, resuspended in IMDM growth media and supplemented with 8 µg/ml polybrene before it was used to infect Hap1 cells.

~1.2x108 Hap1 cells were mutagenized by transduction with retroviral supernatant. 3 T-175 flasks were seeded with 2x107 cells 24 hrs before transduction, and freshly prepared retrovirus was added in two doses 8 hrs apart. Cells were amplified by passaging every 48 hrs, and during each passage cells from all flasks were pooled and 1.2x108 were re-seeded to retain the complexity of the mutagenized library. Fluorescence-activated cell sorting (FACS) revealed that 96% of cells expressed GFP and hence contained at least one GT integration. The screen was started 6 days after GT infection.

 For Dox selection, 1.05x108 mutagenized Hap1 cells were seeded in 12 T-175 flasks 24 hrs before drug treatment, and were exposed to 17.5 nM Dox in IMDM growth media. Dox-containing media was refreshed after 48 hrs. After 4 days of treatment, cells were washed twice with PBS and expanded in IMDM growth media without Dox. 1.5x108 cells were harvested, of which 3x107 cells were used to prepare an experimental sequencing library. 3x107 unselected cells were used to prepare a reference sequencing library.

 Sequencing libraries for both the experimental and control cell populations were prepared and deep sequenced as described previously (see “Sequence analysis of the GT insertion sites in the unselected mutagenized cell population” methods section in reference ([2](#_ENREF_2))). All GT insertions were mapped as described previously (see “Analysis of GT insertions in the unselected mutagenized cell population” methods section in reference ([2](#_ENREF_2))), and the significance of GT enrichment in the selected compared to the control cell populations was calculated as described previously (see “Sequence analysis of GT insertion sites” methods section in reference ([1](#_ENREF_1))).

**Isolation clonal cell lines carrying specific genetrap insertions**

Hap1 mutant cell lines containing GT insertions of interest were isolated as follows. Mutagenized Hap1 selected with Dox were single-cell sorted into 16 96-well plates and colonies were grown for 17 days. Cells were harvested, a portion of each clone was passaged for continuous growth, and the remainder of the cells from adjacent pairs of rows in each plate were pooled. A portion of the cells from pairs of plates were further pooled, so as to obtain 8 “plate-pair” pools, and 64 “row-pair” sub-pools. Cells from plate-pair pools were harvested by centrifugation, genomic DNA was prepared using the QIAamp DNA mini kit (Qiagen, Hilden, Germany) and each pool was probed for clones containing a GT in genes of interest using a nested PCR strategy. A forward primer complementary to a unique sequence in the GT, and reverse primers complementary to unique genomic regions enriched for GT insertions were used: Forward-GT (Genetrap) 5′-GCGGGCAAAGTCCAGAAC-3′, ABCB1\_G1R (Antisense, Reverse) 5′-GCGGGCAAAGTCCAGAAC-3′ and TOP2A\_G1R (Sense, Reverse) 5′-GGAAAAGCCAACTTCACCAG-3′. PCR amplification from 400 ng of genomic DNA was done in 25 µl reactions containing 1 x LongAmp Taq reaction buffer (NEB, Ipswich, MA), 300 µM of each dNTP, 400nM of each primer and 2.5 units of LongAmp Taq DNA polymerase. Once positive plate-pair pools were identified, genomic DNA from the corresponding row-pair sub-pools was prepared using QuickExtract DNA Extraction Soln. 1.0 (Epicentre, Madison, WI) and the PCR procedure was repeated to identify row pairs containing clones of interest. Finally, individual clones were harvested from positive row pairs, and the relevant ones were identified using the same procedure. To map the precise GT location, the final PCR product obtained from individual positive clones was sequenced. To confirm the purity of each clone, the appropriate reverse primer listed above was used together with a corresponding forward primer flanking each GT insertion: Forward ABCB1\_G1F 5′-ACCCTCCACTCTATGGAGTCTTT-3′, Reverse ABCB1\_G1R 5′-GCGGGCAAAGTCCAGAAC-3′ and Forward TOP2A\_G1F 5′-ACCCTCAGCTCAAGAGGCTA-3′, Reverse TOP2A\_G1R 5′-GGAAAAGCCAACTTCACCAG-3′.

**Use of CRISPR/Cas9 methods to introduce frameshift mutations in genes**

 Oligos encoding the guide RNA (gRNAs) for each target gene were chosen from a previously reported library ([4](#_ENREF_4)) and cloned into pSpCas9(BB)-2A-GFP (PX458), obtained from Addgene (Cambridge, MA) and kindly provided by Dr. Feng Zhang ([5](#_ENREF_5)) at MIT. Two different oligos, encoding two different guide RNAs (gRNAs) for each gene, were cloned into PX458 and transfected into early passage Hap1 cells using X-tremeGENE HP transfection reagent. Five days after transfection, single transfected (i.e. GFP-expressing) cells were sorted using FACS into each well of 96 well plates. Colonies that were derived from these single cells were tested for the presence of mutations by Sanger sequencing of an amplicon around the predicted gRNA binding site (Supplementary Table 2) and/or by immunoblotting to test for expression of the protein product of the gene (Figure 2A).

 LentiCRISPR v2 (Plasmid #52961), kindly provided by Dr. Feng Zhang ([6](#_ENREF_6)) and obtained from Addgene, was used for lentiviral delivery of gRNAs and Cas9 to knock-down of *SMARCB1* in cancer cells. The same gRNA oligos used to successfully target *SMARCB1* with PX458 in Hap1 cells were cloned into LentiCRISPR v2. A Control lentiCRISPR vector was constructed using a gRNA sequence directed against an irrelevant mouse gene (*Coronin*). Lentivirus was generated by transient transfection of the viral plasmid and packaging plasmids into 293FT cells. Cancer cell were transduced with the lentivirus by spinfection (500xg for 1.5h) in the presence of Polybrene (10 µg/mL). After 2 days of recovery, transduced cells were selected by exposure of cells to Puromycin (2 µg/mL) for two weeks.

The oligo sequences used to encode gRNAs are as given in the table below. Sequence in black font corresponds to the targeted genomic region while green fonts represent the nucleotides added to the oligos for cloning into PX458 or LentiCRISPR v2.

|  |  |  |
| --- | --- | --- |
| Target Gene | Oligo 1 | Oligo 2 |
| ARID1ACR1 | CACCGGCGGTACCCGATGACCATGC | AAACGCATGGTCATCGGGTACCGCC |
| ARID1ACR2 | CACCGCCCCTCAATGACCTCCAGTA | AAACTACTGGAGGTCATTGAGGGGC |
| SMARCB1CR1 | CACCGAACTACCTCCGTATGTTCCG | AAACCGGAACATACGGAGGTAGTTC |
| SMARCB1CR2 | CACCGTGTGACCCTGTTAAAAGCCT | AAACAGGCTTTTAACAGGGTCACAC |
| SMARCA4CR1 | CACCGGGATCCCTACCTTGTGCATC | AAACGATGCACAAGGTAGGGATCCC |
| SMARCA4CR2 | CACCGCCCGAAGACGGGCCACTGGC | AAACGCCAGTGGCCCGTCTTCGGGC |
| TADA3CR1 | CACCGGGATCCGTGGCACGTCGATA | AAACTATCGACGTGCCACGGATCCC |
| TADA3CR2 | CACCGTCAGTAACTCCTCAAGTGTG | AAACCACACTTGAGGAGTTACTGAC |
| ABCB1CR1 | CACCGTGACAAGTTGTATATGGTGG | AAACCCACCATATACAACTTGTCAC |

 In terms of nomenclature, superscripted CR1 or CR2 after the gene name is used to denote which of the distinct gRNA sequences above were used for gene editing. In some cases, superscripted CR1.1 or CR1.2 denotes two different (1.1 and 1.2) clonal cell lines carrying different null alleles of the gene generated from the CR1 gRNA. As an example, SMARCB1CR1 and SMARCB1CR2 denote two clonal cell lines generated using two different gRNAs CR1 and CR2. SMARCB1CR1.1 and SMARCB1CR1.2 denote two cell lines carrying different frameshift mutations in SMARCB1, but both generated by introduction of the CR1 gRNA.

**Stable expression of epitope-tagged SMARCB1 and SMARCA4**

A plasmid with the human SMARCB1 cDNA was purchased from GE Healthcare (MHS6278-213244628), subcloned into pENTR2B vector along with a 3x-HA tag at C-terminal, and then transferred by gateway cloning to pLenti-CMV-Puro-DEST ([7](#_ENREF_7)) (Plasmid #17452) from Addgene kindly provided by Dr. Eric Campeau. Lentivirus produced in 293FT cells was used to infect cells by spinfection (500xg for 1.5h) and overnight incubation, followed by selection with 2 µg/mL of puromycin for 2 weeks. For SMARCA4, the pQCXIH plasmid expressing human SMARCA4-Flag retroviral plasmid was obtained from Addgene (Plasmid #19148), kindly provided by Dr. Joan Massague ([8](#_ENREF_8)), Memorial Sloan-Kettering Cancer Center, NY and used to make retrovirus using the Phoenix-Ampho packaging cell line according to the suppliers’ instructions. Cells were transduced with the retrovirus by spinfection (500xg for 1.5h), followed by selection for 2 weeks in Hygromycin B (200 µg/mL).

**Cell viability (MTT) assay**

5,000 cells were plated in each well of 96 well plate, allowed to grow for 24 hours and then treated with various concentrations of Dox (or other drugs ) in quadruplicate; the concentration of the solvent (DMSO) in which Drug was dissolved was normalized across all wells to 0.1% (v/v). In MTT experiments, *n* represents four technical replicates i.e. four wells of a 96 well plate. After 93h of Drug exposure, 10 µL of 5 mg/mL MTT reagent was added into each well. Cells were incubated for 3 hrs, media was removed and 50 µL of DMSO was added to each well to solubilize the purple colored formazan. Absorbance was read at 570 nm on Biotek Synergy HT microplate reader. The MTT assay for each cell line was performed at least two independent times, with similar results. SigmaPlot was used to plot the dose response curve and calculate LC50 value. Data was normalized for each case by considering absorbance from untreated cells as maximum and cells treated with highest conc. of drug as minimum. Equation used for plotting is: Four Parameter Logistic Curve,y = min + (max-min)/(1 + (x/LC50)^(-Hillslope)).

**Long term growth assay**

105 cells were plated in each well of a six well plate. After 24 hrs the cells were treated with 17.5 nM or 30 nM Dox for 10 days. Media was refreshed every 3 days during the course of the experiment to prevent Dox depletion. After 10 days, the cells were fixed with 4% Paraformaldehyde (PFA) and stained with 0.05% Crystal violet solution for 1 hr. For each cell line, this clonogenic growth assay was performed at least two independent times.

 For the Dox pulse dosing regimen (Figure 5E), 5,000 cells were plated in each well of a 12 well plate. Replicates (n=3) refer to technical replicates, with each cell lines plated and treated identically in three different wells of a 12 well plate. Identical results were obtained when the entire experiment was repeated a second time at an initial plating density of 50,000 cells/well (again in triplicate). After 24 hrs of growth, cells were treated with 0.25 µM, 0.5 µM and 1.0 µM Dox for 2 hrs, after which the Dox-containing media was removed and replaced with fresh media lacking the drug. Cells were grown for 10 days, fixed with 4% PFA and stained with crystal violet solution. To quantitate crystal violet staining in each well, the plates were scanned and ImageJ used to determine the background-corrected integrated density.

**Immunoblotting**

Cells were scraped into ice-cold phosphate buffered saline (PBS) containing 1x Sigma Fast Protease Inhibitor Cocktail (Roche) and collected as a pellet by centrifugation (500xg, 5 min, 4°C). Cells were lysed (45 min., 4°C) by agitation in modified RIPA buffer (50 mM sodium-Tris pH 8.0, 150 mM sodium chloride, 2% NP-40, 0.25% deoxycholate, 0.1% sodium-dodecyl sulfate (SDS), 1mM sodium fluoride, 1 mM dithiothreitol (DTT), 1x Sigma Fast Protease Inhibitor Cocktail (Roche) and 10% glycerol), followed by centrifugation at 20,000xg for 30 min. at 4°C and determination of the total protein concentration in each lysate using the Pierce BCA Protein Assay Kit (Thermo Scientific, Rockford, IL). 50 µg of each lysate was fractionated by 8% PAGE, transferred to nitrocellulose membrane and blocked with 0.1% Casein in 0.2x PBS for 1 hr at room temperature. Membranes were incubated with protein-specific antibodies overnight at 4°C and followed by either HRP-conjugated secondary antibodies (Figure 1) or with fluorophore-conjugated secondary antibodies (Figures 2,4,5,6 and Supplementary Figure 4) for quantitative imaging using the Li-COR Odyssey system. Each immunoblotting experiment was performed at least two times with different passages of each cell line.

**Quantitative real-time PCR (qRT-PCR)**

RNA was extracted with Trizol (Invitrogen) from cells grown to ~70% confluency in 6-well plates and converted into cDNA using the iScript cDNA synthesis kit (Bio Rad). Quantitative real-time PCR assays were performed on cDNA with the IQ SYBR Green Supermix (Bio Rad) using ABI-7900HT sequence detector (Applied Biosystems). Primer pairs used for qRT-PCR are given below. Ct values were normalized relative to *GAPDH* levels for each sample. Replicates (n=3) refer to measurements made in three different qRT-PCR reactions. Each experiment was performed at least twice.

|  |  |  |
| --- | --- | --- |
| Gene | Forward Primer | Reverse Primer |
| *ABCB1* | TTGCTGCTTACATTCAGGTTTCA | AGCCTATCTCCTGTCGCATTA |
| *TOP2A* | ACC ATTGCAGCCTGTAAATGA | GGGCGGAGCAAAATATGTTCC |
| *SMARCB1* | GCGAGTTCTACATGATCGGCT | CACAGTGGCTAGTCGCCTC |
| *SMARCA4* | AATGCCAAGCAAGATGTCGAT | GTTTGAGGACACCATTGACCATA |
| *ARID1A* | GGCGGGACTAACCCATACTC | GGCCCTGTT GAC CATACCC |
| *GAPDH* | AAAGGGTCATCATCTCTG | GCTGTTGTCATACTTCTC |

**Dox uptake assay**

For Dox uptake in bulk cell populations using a fluorescence microplate reader (Figure 1E), 25,000 cells were plated in each well of a 96 well plate in triplicate (*n*=3). After 24 hrs the cells were treated with Dox for 2 hrs, washed twice with PBS and lysed in 50 µL of 10 mM Tris, pH 8.0, 1% SDS at RT for 20 minutes. Dox fluorescence in the lysate was measured on a Biotek Synergy HT (Ex: 485 nm Em: 590 nm).

 For single-cell Dox and Rhodamine experiments using FACS (Supplementary Figure 4D and 4E), cells at 70% confluence were treated with Dox for 2 hrs or Rhodamine-123 for 1 hr. Both Rhodamine-123 treated cells and Dox treated cells were harvested using Trypsin for 5 min, chilled to 4°C in media and analyzed for Rhodamine-123 or Dox fluorescence by FACS on a BD Fortessa.

**RNA-seq**

Cells were grown to 70% confluency and RNA was extracted using Trizol (Invitrogen). Library preparation and sequencing was done in Stanford Functional Genomics Facility. In brief, a KapaBiosystems Stranded mRNA kit was used for library preparation. Four unique Illumina adapters (Bar Coded) for multiplexing were used. Illumina NextSeq was used for sequencing. Two biological replicates were analyzed for each cell type. The raw data obtained was aligned, quantified and analyzed by using Partek® Flow® software, version 4.0, Partek Inc., St. Louis, MO, USA. Reads were aligned to human reference genome build hg19 using STAR Align and Quantify pipeline in Partek Flow ([9](#_ENREF_9)). Differential gene expression (GSA) analysis was done using RPKM normalization. Generally, for the analysis of differential gene expression only the genes having P-value with false discovery rate (FDR) (step-up) < 0.001 were taken into consideration. To filter out genes with low expression levels an additional filter of Total read count of >1,000 (from all the replicates and cell types) for each gene was used. Heat-maps were generated by importing data from Partek Flow into Partek Genomic Suite 6.6 software, Partek Inc., St. Louis, MO, USA.

 For the gene-expression analysis shown in Figure 3, biological replicates for the SMARCB1 and SMARCA4 null cell lines represent two independent clonal cell lines generated by CRISPR methods using two different guide RNAs. For the WT Hap1 cells and cells null for both SMARCB1 and SMARCA4 (Supplementary Figure 5), replicates used for RNAseq were derived from two different passages of each cell line.

The data discussed in this publication have been deposited in NCBI's Gene Expression Omnibus and are accessible through GEO Series accession number GSE75515 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE75515).

**Correlating SMARCB1 and ABCB1 expression levels using TCGA data**

We used gene expression data for 12 cancer sites: adrenocortical carcinoma (ACC), breast cancer (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), liver hepatocellular carcinoma (LIHC), lung squamous cell carcinoma (LUSC), ovarian serous cystadenocarcinoma (OV), prostate adenocarcinoma (PRAD), sarcoma (SARC), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), available at the TCGA data portal. The data used are summarized below:

|  |  |  |
| --- | --- | --- |
| Cancer | Number of genes | Number of samples |
| ACC | 14,843 | 79 |
| BRCA | 16,021 | 1,093 |
| CESC | 15,642 | 302 |
| HNSC | 15,831 | 520 |
| KIRC | 16,123 | 532 |
| LIHC | 14,906 | 367 |
| LUSC | 16,219 | 501 |
| OV | 17,814 | 541 |
| PRAD | 16,266 | 497 |
| SARC | 15,282 | 259 |
| STAD | 16,222 | 9 |
| THCA | 15,995 | 501 |

These data are produced using RNA sequencing for all cancers, except ovarian cancer for which the data are produced using Agilent microarrays. Pre-processing was performed by log-transformation and quantile normalization of the arrays, and Combat was applied for batch correction ([10](#_ENREF_10)). A Pearson test was used to analyze the association between the expression of SMARCB1 and ABCB1. We report both the p-value of the test (significant if smaller than 0.05) and the Pearson correlation coefficient, corresponding to a measure of the linear correlation between these two variables. Scatter plots depicting data for each of these cancers are shown in correlations Supplementary Figure 2 with all scatterplots).

 As an alternate way to depict the relationship between ABCB1 and SMARCB1 expression, we also discretized the patients in 4 groups according to their SMARCB1 level of expression (Box and whisker plots in Supplementary Figure 2). A Wilcoxon test was used to quantify the differences between the ABCB1 expression levels between samples in the top and bottom quartiles (top and bottom 25%) of SMARCB1 expression. The p-values (significant if smaller than 0.05) obtained after running these tests can be found in Supplementary Figure 2.

**Correlating SMARCB1 expression with Dox resistance levels using TCGA data**

A previous study([11](#_ENREF_11)) focused on the identification of changes in gene expression associated with doxorubicin resistance in MCF7 breast cancer cell lines. A list of 41 genes with significantly different expression (absolute fold change > 3) was found, 27 of them being up-regulated and 14 down-regulated in doxorubicin resistant cell lines.

 We used this gene signature to investigate the association of SMARCB1 with resistance to doxorubicin in the twelve cancer sites described above. We first defined a score for this gene signature by taking the difference between the averaged expression of genes positively correlated with drug resistance (fold change > 0) and negatively correlated with drug resistance (fold change < 0):

$$score= \frac{1}{41}\left(\sum\_{Fold change>0}^{}expression+ \sum\_{Fold change<0}^{}expression\right)$$

We then used a Pearson test to measure the association between the expression of SMARCB1 and the score of gene signature. The obtained results (p-value of the test and correlation) can be are representing by the scatterplots shown in Supplementary Figure 3.

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