Supplemental Information

Single-cell analyses of transcriptional heterogeneity during drug tolerance transition in cancer cells by RNA sequencing

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Author Footnotes

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Figure S1. The number of SNVs detected in single cells and population regions cells at various depth of read coverage. Related to Figure 2. The number of SNVs was normalized by the number of genomic bases with the corresponding depth of read coverage to ensure that the difference in the number of SNVs was not due to the difference in the breadth of genome coverage.

Figure S2. Number of bases with reads at various depth of coverage. Related to Figure 2. The number of bases with reads in different genomic regions presenting low to high depth of sequencing was plotted to detect biases in coverage/depth of sequencing between single cells vs. cell population RNA-Seq data.

Figure S3: The fraction of novel variants shared between any two single cells. Related to Figure 2. A high heterogeneity is observed between single cells within and between groups. UNT: untreated cells, S: stressed cells, DT: drug-tolerant cells.

Figure S4. Hierarchical clustering of the top 50 most differentially expressed genes. Related to Figure 4.
(A) Hierarchical clustering of the 50 most significant differential expressed genes between stressed- and drug-tolerant cells (p-value < 0.001, FDR < 0.025). (B) Hierarchical clustering of the 50 most significant differential expressed genes between untreated- and drug-tolerant cells (p-value < 0.001, FDR < 0.025).

Figure S5. Hierarchical clustering of gene expression data. Related to Figure 4
(A) Hierarchical clustering of gene expression data for single-cells in Euclidean distance with 1,000 bootstrap replications. Values at branches are approximately unbiased (AU) p-values (left), bootstrap probability (BP) values (right), and single-cell labels (bottom). (B) The clustering gene expression data in adjusted-RPKM using principal component analysis (PCA) showed that gene expression profiles of stressed cells (red) were much different from those of untreated (green) and drug-tolerant cells (black). UNT_1-5: untreated single cells, UNT_POP: untreated population cells, UNT_Pooled: untreated 5-cell pooled sample. S: stressed: DT: drug-tolerant.

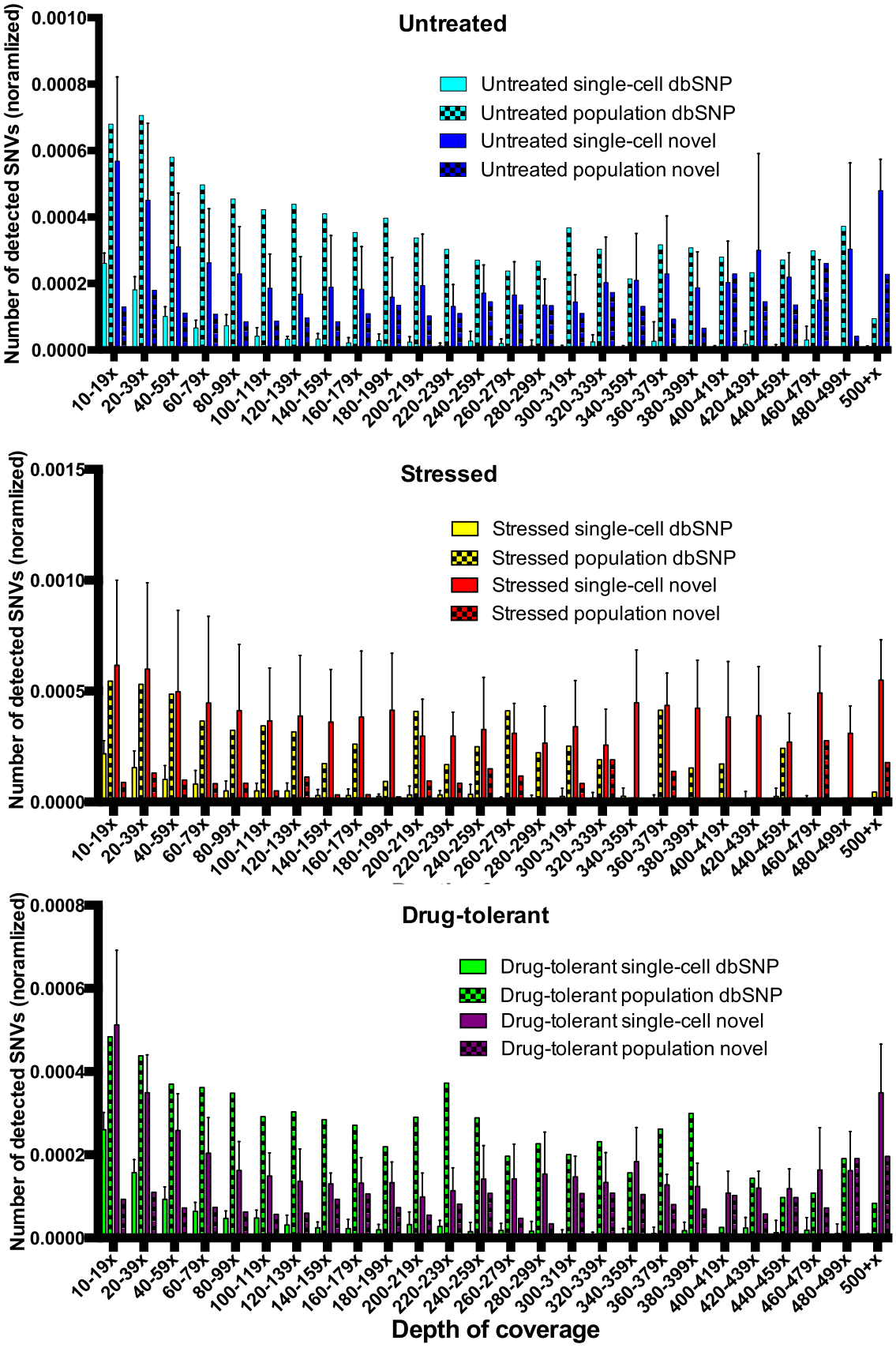
Figure S6. Single cell gene expression is not reflected from averaged expression. Related to Figure 4. (A) Scatter plots of averaged gene expression for pair-wise comparison between 5 single cells in untreated, stressed and drug-tolerant cell groups. (B) Scatter plots of gene expression between monoclonal (<6 cell divisions apart) drug-tolerant single cells. Comparison between two drug-tolerant (DT) cells (left and right panel); One DT cell vs. four DT cells comparison (middle panel). (C) Scatter plots of gene expression between stressed cells and drug-tolerant cells. One-to-one comparison for stressed (S) cells (left panel); One S cell vs. four S cells (middle panel); One S cell vs four DT (right panel).

Figure S7. Comparing single-cell SNV frequencies between cells from normal human cells and cancer cell line cells. Related to Figure 2. The single-cell SNV frequencies are calculated by dividing the number of private novel SNVs in a single cell by the total number of novel SNVs in that cell. Private novel SNVs are unique SNVs only present in the single cell and not in any other single cell of the same type type. We utilized the single-cell RNA-Seq data from Yan et al., 2013 including three oocytes, one pair of 2-cell embryo cells, and two sets of four single cells from a 4-cell embryo. From Ramsköld et al., 2012 single-cell RNA-Seq dataset, we analyzed two sets of single cells from two different melanoma cancer cell lines (UACC257 and SKMEL5), and eight human embryonic stem cells.

Figure S8. Hierarchical clustering of the expressed genes involved in cell-cycle, DNA-damage signaling, senescence, drug-resistance and metabolism, and apoptosis between untreated- (blue), stressed-arrested (red) and drug-tolerant cells (green). Related to figure 4.

Figure S9. Transcript abundance for genes that have an RNA variant in at least 3 of the drug-tolerant cells shown in Table 1. Related to Table 1. Relative expression compared to the total RNA abundance was determined as adj-RPKM, as described. UNT: untreated, S: stressed, DT: drug-tolerant.

Figure S1, Lee & Lopez-Diaz et al



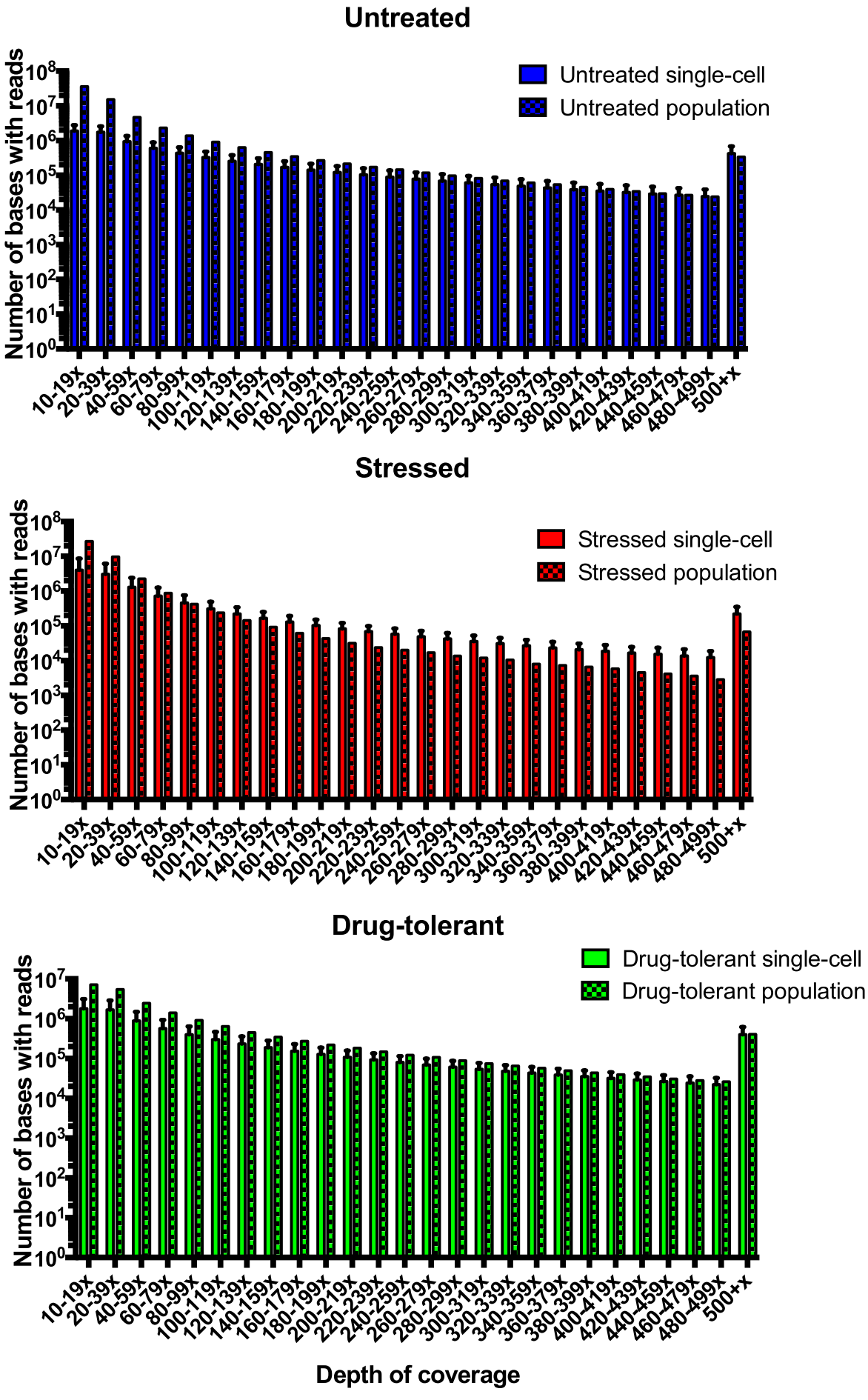

Untreated
Untreated single-cell
Untreated population
Number of bases with reads
Stressed
Stressed single-cell
Stressed population
Drug-tolerant
Drug-tolerant single-cell
Drug-tolerant population
10-19x
20-39x
40-59x
60-79x
80-99x
100-119x
120-139x
140-159x
160-179x
180-199x
200-219x
220-239x
240-259x
260-279x
280-299x
300-319x
320-339x
340-359x
360-379x
380-399x
400-419x
420-439x
440-459x
460-479x
480-499x
500+x
Depth of coverage

Figure S3, Lee & Lopez-Diaz et al

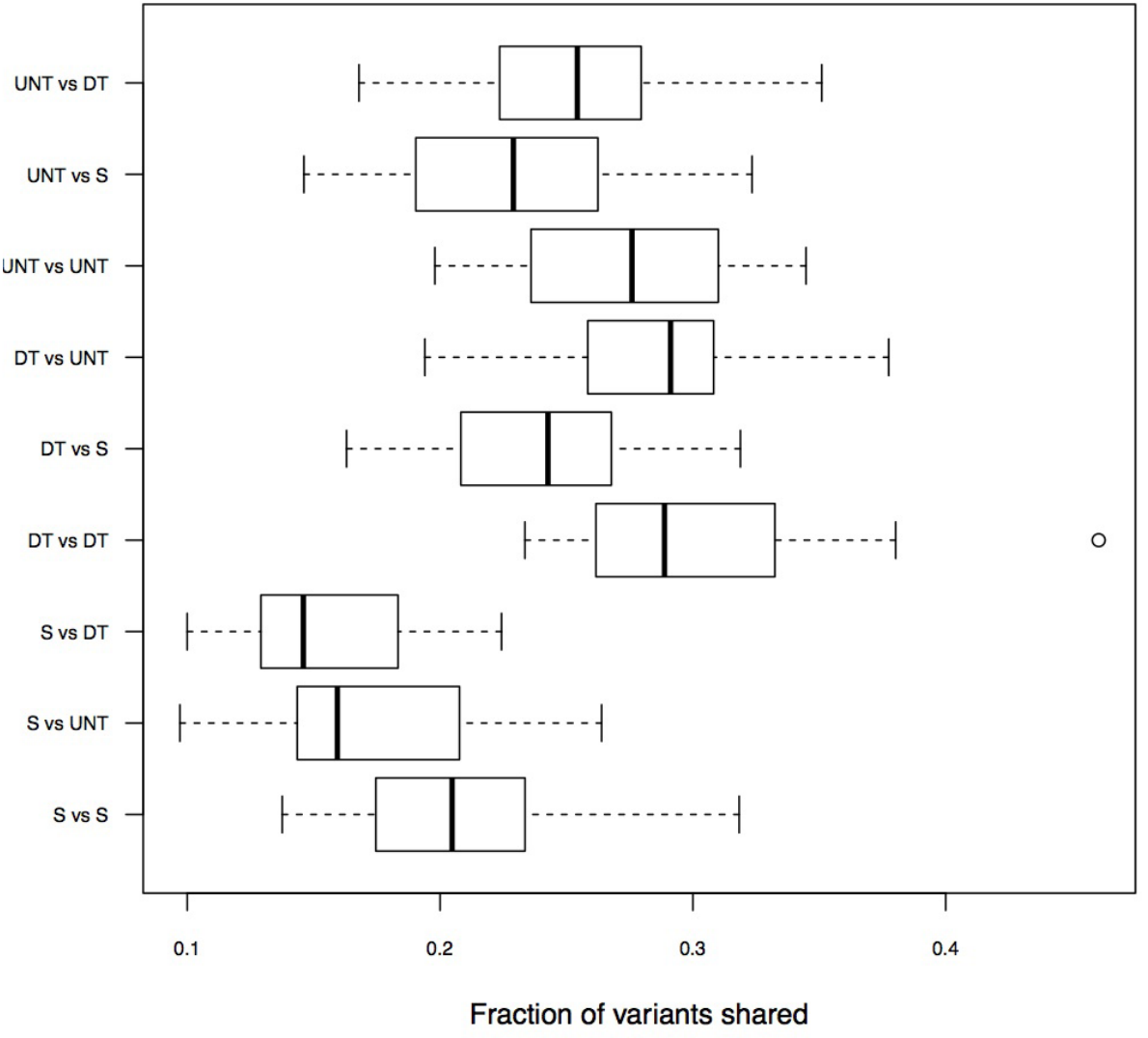


Figure S4, Lee & Lopez-Diaz et al.

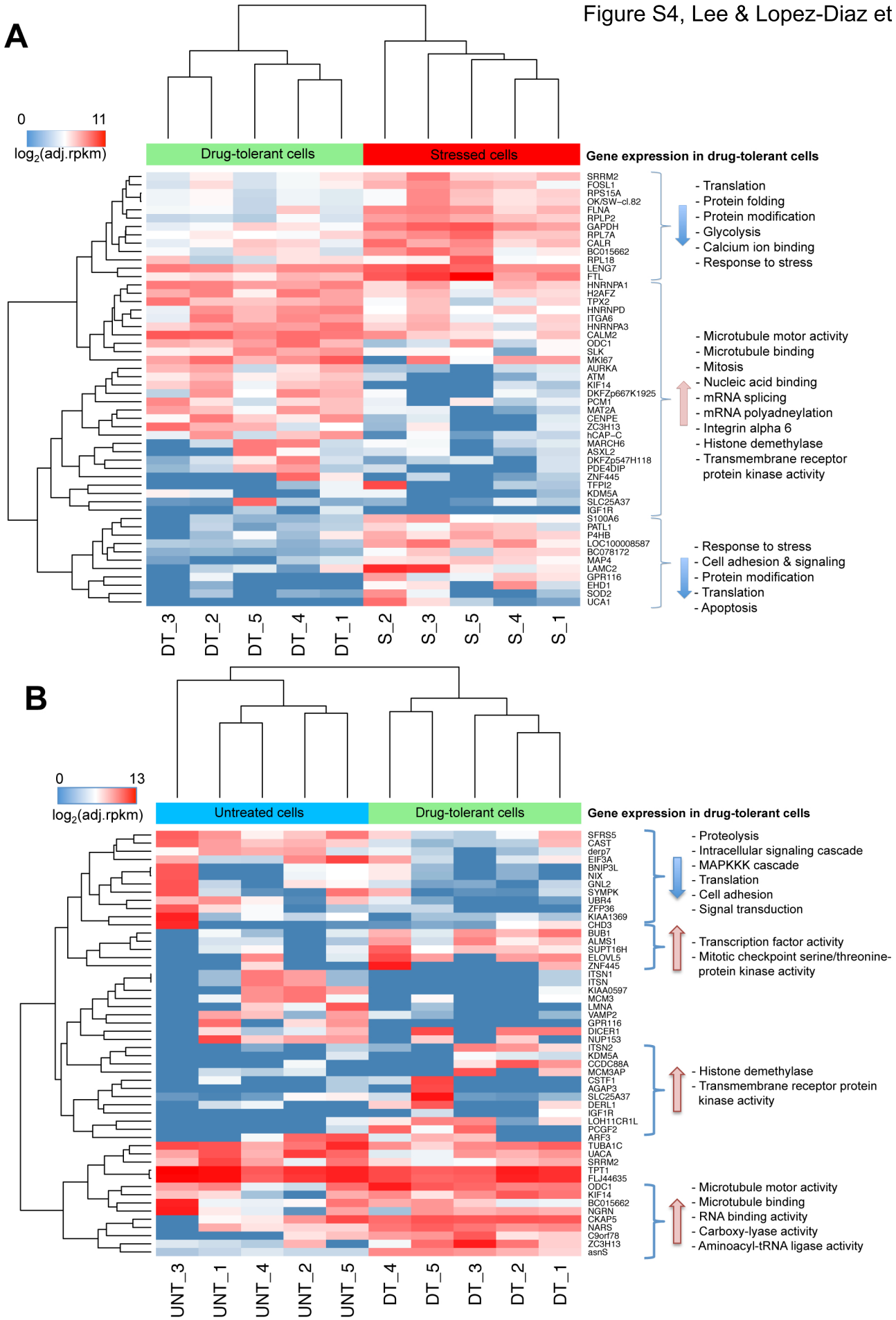
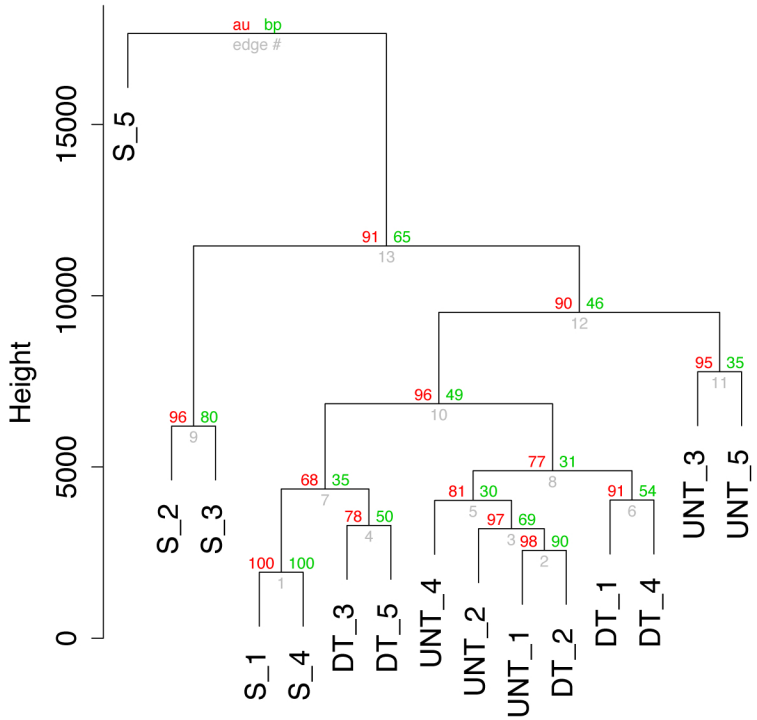
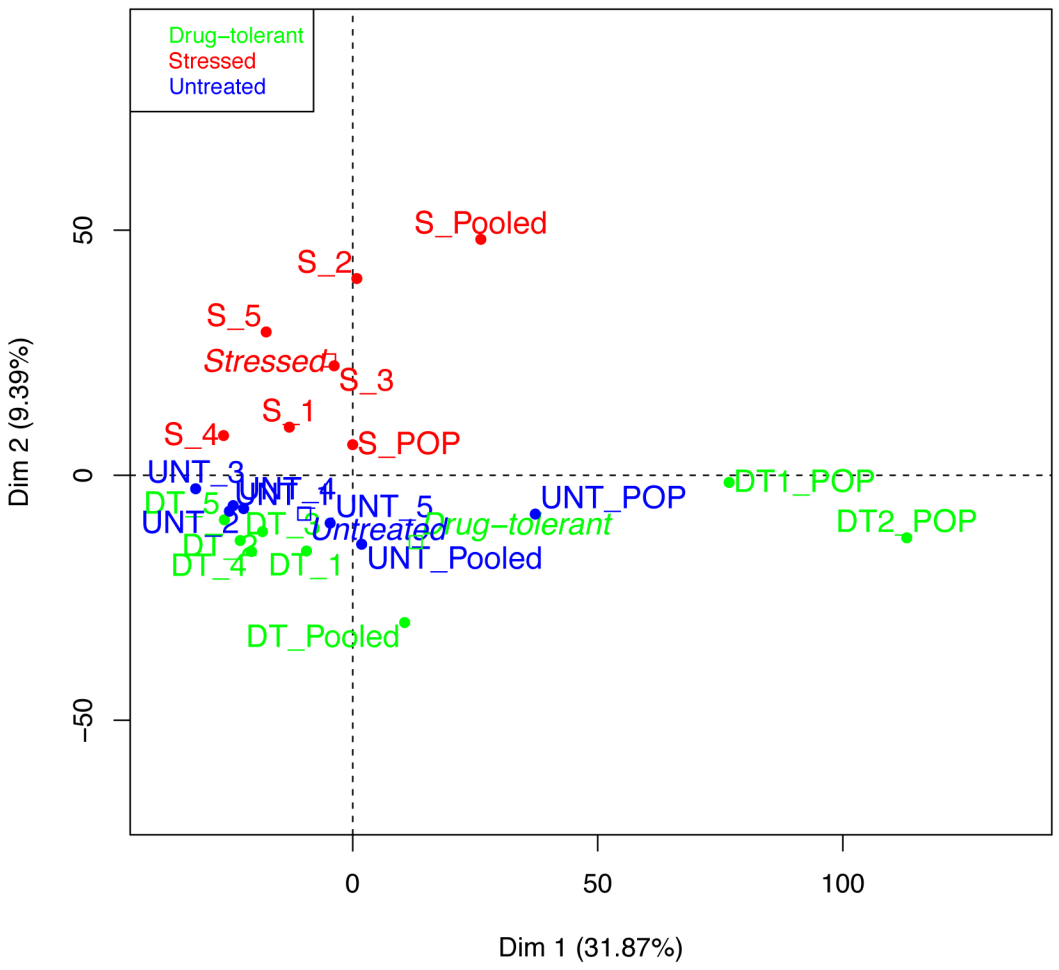


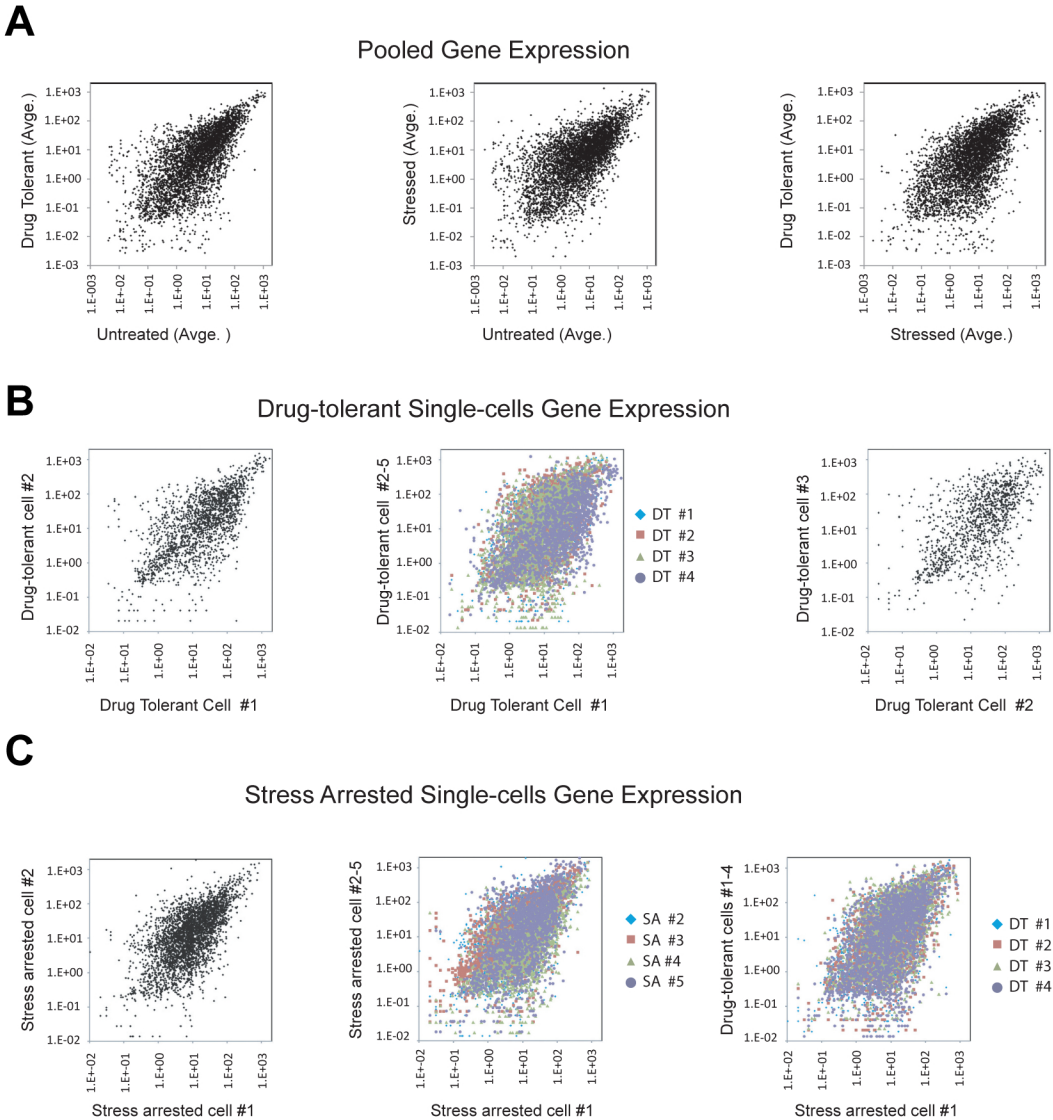
Figure S5, Lee & Lopez-Diaz et al

A



B




A
Pooled Gene Expression
Drug Tolerant (Avge.)
Untreated (Avge.)
Stressed (Avge.)
Untreated (Avge.)
Drug Tolerant (Avge.)
Stressed (Avge.)
B
Drug-tolerant Single-cells Gene Expression
Drug-tolerant cell #2
Drug Tolerant Cell #1
Drug-tolerant cell #2-5
Drug Tolerant Cell #1
DT #1
DT #2
DT #3
DT #4
Drug-tolerant cell #3
Drug Tolerant Cell #2
C
Stress Arrested Single-cells Gene Expression
Stress arrested cell #2
Stress arrested cell #1
Stress arrested cell #2-5
Stress arrested cell #1
SA #2
SA #3
SA #4
SA #5
Drug-tolerant cells #1-4
Stress arrested cell #1
DT #1
DT #2
DT #3
DT #4

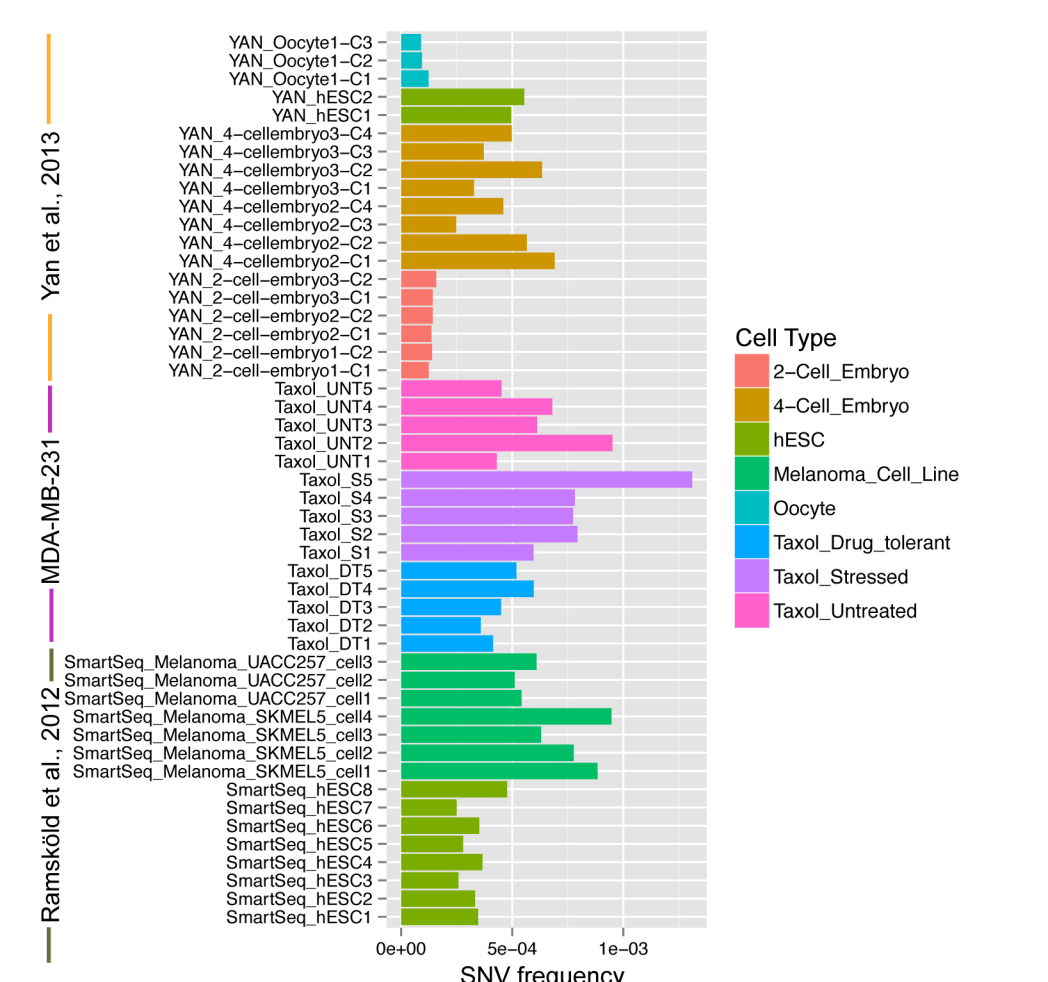
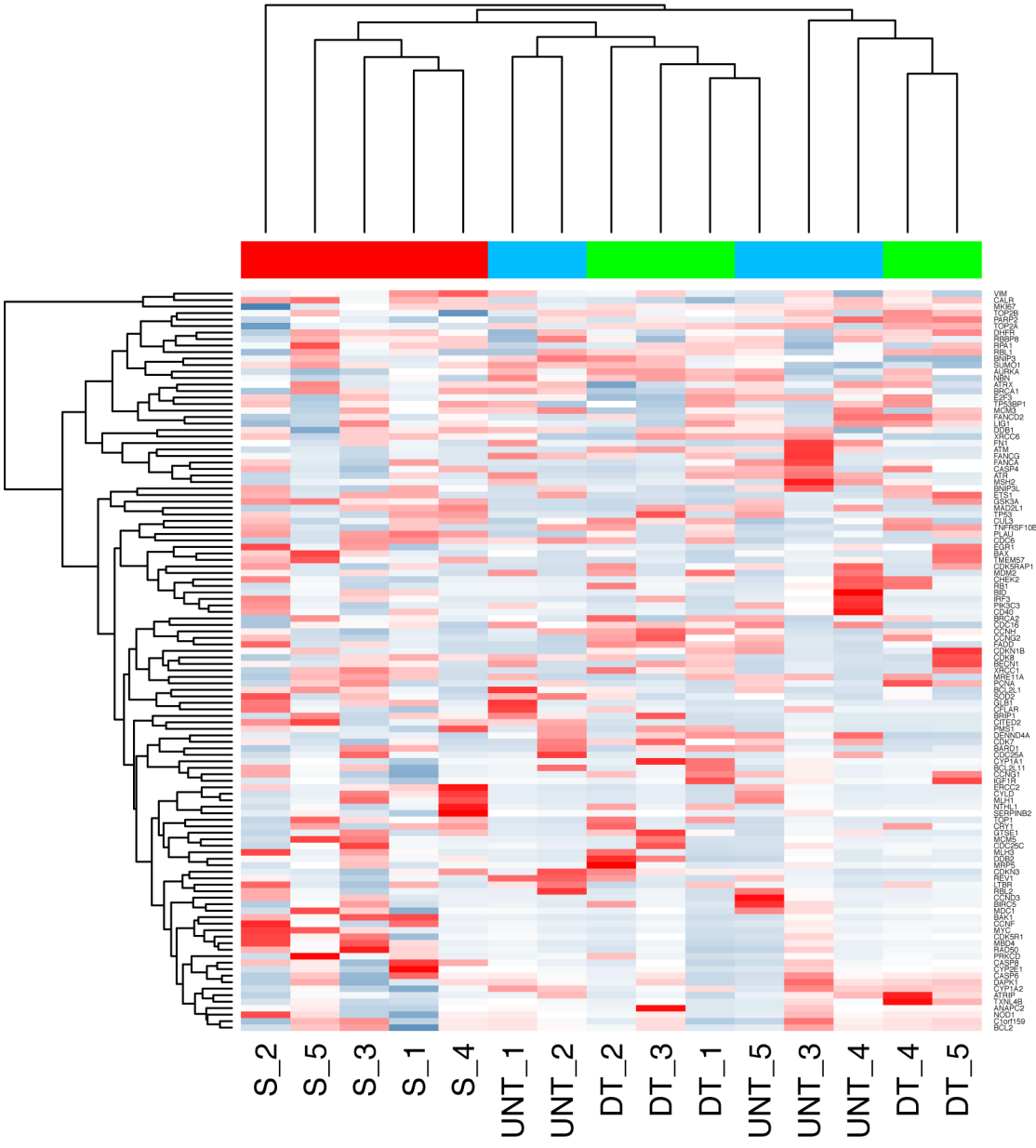
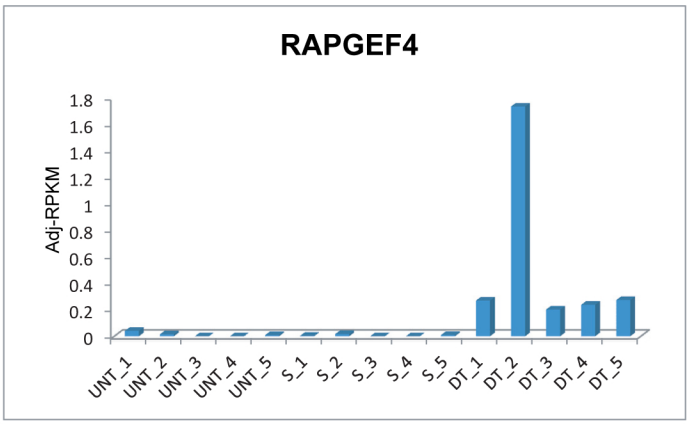
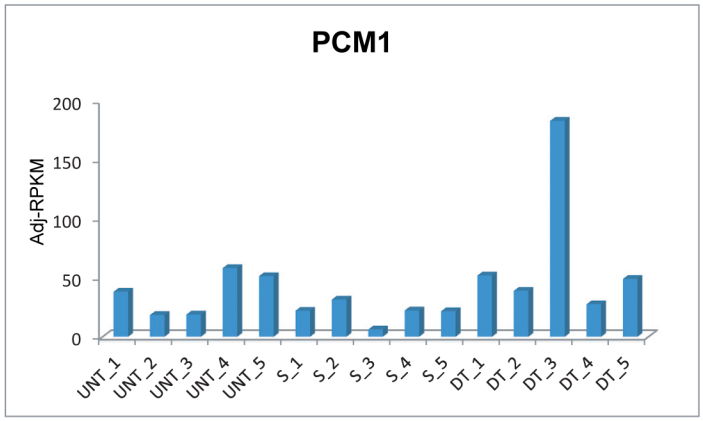


Figure S7, Lee & Lopez-Diaz et al.

Figure S8, Lee & Lopez-Diaz et al.




RAPGEF4
Adj-RPKM
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
UNT_1
UNT_2
UNT_3
UNT_4
UNT_5
S_1
S_2
S_3
S_4
S_5
DT_1
DT_2
DT_3
DT_4
DT_5


PCM1
Adj-RPKM
200
150
100
50
0
UNT_1
UNT_2
UNT_3
UNT_4
UNT_5
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S_2
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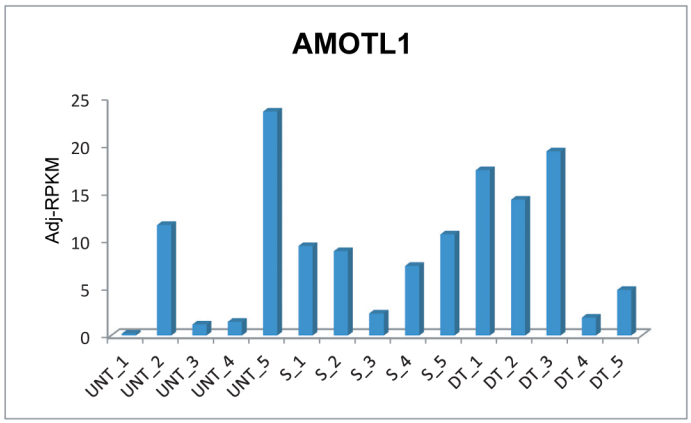
S_4
S_5
DT_1
DT_2
DT_3
DT_4
DT_5


AMOTL1
Adj-RPKM
25
20
15
10
5
0
UNT_1
UNT_2
UNT_3
UNT_4
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S_2
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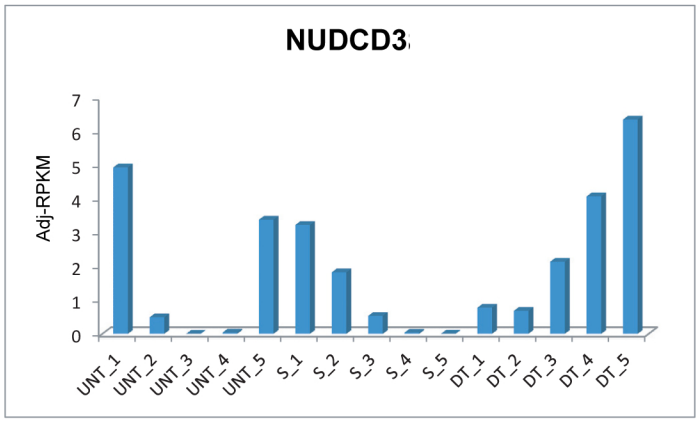
S_4
S_5
DT_1
DT_2
DT_3
DT_4
DT_5


NUDCD3
Adj-RPKM
7
6
5
4
3
2
1
0
UNT_1
UNT_2
UNT_3
UNT_4
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S_1
S_2
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S_5
DT_1
DT_2
DT_3
DT_4
DT_5

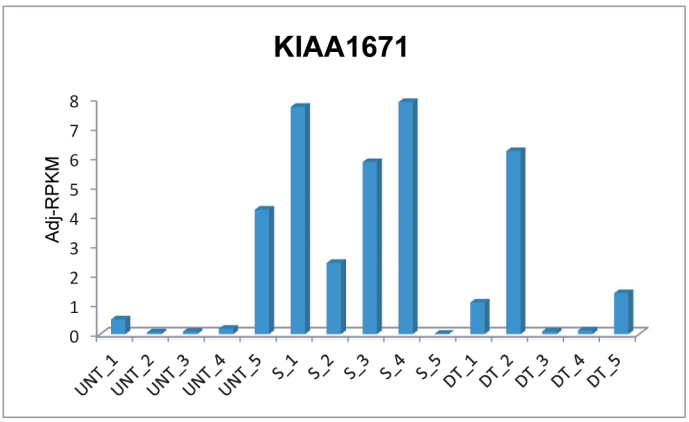
KIAA1671
Adj-RPKM
8
7
6
5
4
3
2
1
0
UNT_1
UNT_2
UNT_3
UNT_4
UNT_5
S_1
S_2
S_3
S_4
S_5
DT_1
DT_2
DT_3
DT_4
DT_5

Table S1. Number of sequencing reads and mapping statistics.

Samples	Total number of paired-end reads sequenced	Total mapped reads without PCR duplicates, properly paired
UNT_1	72,398,342	42,429,918
UNT_2	97,896,104	69,651,740
UNT_3	32,434,019	25,731,672
UNT_4	86,764,133	62,280,876
UNT_5	55,056,490	22,804,666
UNT_Pop	94,393,218	80,834,490
S_1	93,752,892	89,363,318
S_2	77,374,749	59,347,478
S_3	57,117,251	27,832,072
S_4	76,309,928	56,447,554
S_5	63,019,868	46,954,348
S_Pop	89,785,654	73,548,017
DT_1	94,547,328	47,021,098
DT_2	86,555,396	46,399,478
DT_3	69,507,808	43,944,268
DT_4	86,185,154	66,641,812
DT_5	105,928,132	61,132,450
DT_Pop_1	110,801,220	85,512,326
DT_Pop_2	106,855,138	70,235,819

Table S2. RNA sequencing reads of the population cells cover more genomic region than that of single cells.

	Samples	% Genomic coverage
Single cells	UNT_1	6.5%
	UNT_2	7.1%
	UNT_3	2.2%
	UNT_4	6.5%
	UNT_5	11.0%
	S_1	20.9%
	S_2	14.2%
	S_3	12.1%
	S_4	5.1%
	S_5	5.1%
	DT_1	9.9%
	DT_2	6.1%
	DT_3	3.9%
	DT_4	5.5%
	DT_5	5.8%
Population	UNT_POP	49.5%
	S_POP	48.2%
	DT_POP_1	36.7%
	DT_POP_2	41.9%

For each sample, the percent genomic coverage is calculated by dividing the total number of transcriptomic-bases with at least 1x read coverage by the total number of transcriptomic bases.

Table S3. Number of genes with RPKM>1 and adjRPKM>1 in single cells and population cells

Samples	Number of genes with RPKM>1	% detected genes compared to population	Number of genes with adj-RPKM>1	% detected genes compared to population
UNT_1	2484	20%	2212	17%
UNT_2	2431	19%	2172	17%
UNT_3	1266	10%	959	7%
UNT_4	2288	18%	2040	16%
UNT_5	3635	29%	3070	24%
UNT_Pooled_5cells	8175	65%	10146	79%
UNT_Pop	12541	-	12854	-
S_1	4442	32%	4565	38%
S_2	3992	29%	3835	32%
S_3	3869	28%	3383	28%
S_4	2011	15%	1665	14%
S_5	1909	14%	1644	14%
S_Pooled_5cells	10209	74%	12855	107%
S_Pop	13796	-	12007	-
DT_1	3261	24%	2927	25%
DT_2	2641	20%	2137	18%
DT_3	2091	15%	1564	13%
DT_4	2247	17%	1902	16%
DT_5	2310	17%	1879	16%
DT_Pooled_5cell	8175	60%	9760	82%
DT_Pop_1	12443	-	11981	-
DT_Pop_2	14609	-	11795	-

Table S4. The number of common and unique SNVs detected in single cells and population in three different groups. Related to Figure 2.

Cell Type	Cell ID	All SNVs in single cell passed all filters	All SNVs in population passed all filters	Comparable SNVs in single cell	Comparable SNVs in population	Novel SNVs only in single cell	Novel SNVs only in population	Novel SNVs in both single cell and population	dbSNP variants only in single cell	dbSNP variants only in population	dbSNP variants in both single cell and population
Untreated	1	6284	63578	2109	2411	1356	470	760	28	93	663
	2	8382	63578	3097	2809	2270	516	834	36	104	715
	3	2267	63578	784	451	644	107	142	15	17	116
	4	7595	63578	2257	2155	1602	402	658	35	108	566
	5	4000	63578	2292	2919	1292	545	1003	33	144	877
Stressed	1	13756	35227	5278	5439	3211	824	2071	59	309	1897
	2	8886	35227	4832	2967	3641	392	1196	34	127	1086
	3	6152	35227	2902	2000	2217	336	687	23	142	623
	4	4342	35227	1850	1025	1464	152	392	31	58	351
	5	5748	35227	2873	1021	2442	139	435	30	42	390
Drug-tolerant	1	8100	11857	2112	1913	1343	363	773	31	98	683
	2	3684	11857	1280	1248	780	251	503	14	63	442
	3	2688	11857	965	728	677	137	289	11	28	251
	4	6933	11857	1630	977	1233	186	401	18	43	349
	5	4315	11857	1336	955	992	199	348	11	50	305

Comparable SNVs are the variants located in genomic regions where there is at least 10x RNA read coverage in both the single cell and the population. SNVs variants in single cell and/or in population are parts of the comparable SNVs. SNVs consist of novel and dbSNP variants.

Table S5. Novel RNA variants found in single cells of early human embryos and human embryonic stem cells from Zang et al., 2013 dataset

Cell1 and cell2 comparison	Shared novel variants	Novel variants only in cell1	Novel variants only in cell2	% Novel shared in cell1	% Novel shared in cell2	% Private variants in cell1	% Private variants in cell2
Oocyte1-C1 and Oocyte1-C2	2441	721	565	77.20%	81.20%	22.80%	18.80%
Oocyte1-C1 and Oocyte1-C3	2277	672	472	77.21%	82.83%	22.79%	17.17%
Oocyte1-C2 and Oocyte1-C3	2289	566	493	80.18%	82.28%	19.82%	17.72%
2-cell-embryo1-C1 and 2-cell-embryo2-C1	2455	732	827	77.03%	74.80%	22.97%	25.20%
2-cell-embryo1-C1 and 2-cell-embryo2-C2	2580	740	953	77.71%	73.03%	22.29%	26.97%
2-cell-embryo1-C1 and 2-cell-embryo3-C1	2290	813	1006	73.80%	69.48%	26.20%	30.52%
2-cell-embryo2-C1 and 2-cell-embryo2-C2	2546	821	934	75.62%	73.16%	24.38%	26.84%
2-cell-embryo2-C1 and 2-cell-embryo3-C1	2242	888	1000	71.63%	69.15%	28.37%	30.85%
2-cell-embryo2-C2 and 2-cell-embryo3-C1	2323	1012	997	69.66%	69.97%	30.34%	30.03%
4-cellembryo1-C1 and 4-cellembryo1-C2	2747	3548	3833	43.64%	41.75%	56.36%	58.25%
4-cellembryo1-C1 and 4-cellembryo1-C4	2406	3088	3274	43.79%	42.36%	56.21%	57.64%
4-cellembryo1-C2 and 4-cellembryo1-C4	2304	3287	3075	41.21%	42.83%	58.79%	57.17%
4-cellembryo2-C1 and 4-cellembryo2-C1	2396	2759	2472	46.48%	49.22%	53.52%	50.78%
4-cellembryo2-C1 and 4-cellembryo2-C3	2395	2862	1524	45.56%	61.11%	54.44%	38.89%
4-cellembryo2-C1 and 4-cellembryo2-C4	2439	2906	2552	45.63%	48.87%	54.37%	51.13%
4-cellembryo2-C2 and 4-cellembryo2-C3	2317	2634	1627	46.80%	58.75%	53.20%	41.25%
4-cellembryo2-C2 and 4-cellembryo2-C4	2446	2791	2812	46.71%	46.52%	53.29%	53.48%
4-cellembryo2-C3 and 4-cellembryo2-C4	2373	1708	2792	58.15%	45.94%	41.85%	54.06%
4-cellembryo3-C1 and 4-cellembryo3-C2	2555	1713	2895	59.86%	46.88%	40.14%	53.12%
4-cellembryo3-C1 and 4-cellembryo3-C3	2370	1572	1514	60.12%	61.02%	39.88%	38.98%
4-cellembryo3-C1 and 4-cellembryo3-C4	2663	1872	2489	58.72%	51.69%	41.28%	48.31%
4-cellembryo3-C2 and 4-cellembryo3-C3	2333	2623	1445	47.07%	61.75%	52.93%	38.25%
4-cellembryo3-C2 and 4-cellembryo3-C4	2598	2961	2390	46.74%	52.09%	53.26%	47.91%
4-cellembryo3-C3 and 4-cellembryo3-C4	2433	1499	2160	61.88%	52.97%	38.12%	47.03%
ESCp0-1-C1 and ESCp0-1-C2	2656	1271	1469	67.63%	64.39%	32.37%	35.61%

Table S6. Comparing single cell SNVs frequencies between cell line cells and normal human cells.

	Single cell	Single-cell RNA variant frequency	Mutation frequency ratio (cell-line vs human oocytes)	Avg. RNA variant frequency	Avg. RNA variant frequency/cell division	Avg.deviation
MDA-MB-231 cells Paclitaxel-paradigm	UNT1	4.30E-04	6.1	6.27E-04		1.55E-04
	UNT2	9.51E-04	13.6			
	UNT3	6.12E-04	8.7			
	UNT4	6.80E-04	9.8			
	UNT5	4.52E-04	6.5			
	S1	5.96E-04	8.5	8.52E-04		1.99E-04
	S2	7.94E-04	11.3			
	S3	7.74E-04	11.1			
	S4	7.82E-04	11.2			
	S5	1.31E-03	18.8			
	DT1	4.14E-04	5.9	4.7E-04	7.8E-05	7.2E-05
	DT2	3.58E-04	5.1			
	DT3	4.50E-04	6.4			
	DT4	5.97E-04	8.5			
	DT5	5.19E-04	7.4			
Early human embryos (Ref:Yan et al. 2013)	Oocyte1-C1	1.23E-04	1.8	7.0E-05		1.39E-05
	Oocyte1-C2	9.37E-05	1.3			
	Oocyte1-C3	8.95E-05	1.3			
	2-cell-embryo1-C1	1.24E-04	1.8	1.4E-04	1.4E-04	
	2-cell-embryo1-C2	1.39E-04	2.0			
	2-cell-embryo2-C1	1.36E-04	1.9			
	2-cell-embryo2-C2	1.42E-04	2.0			
	2-cell-embryo3-C1	1.42E-04	2.0			
	2-cell-embryo3-C2	1.58E-04	2.3			
	4-cell-embryo2-C1	6.91E-04	9.9	4.7E-04	2.4E-04	1.2E-04
	4-cell-embryo2-C2	5.66E-04	8.1			
	4-cell-embryo2-C3	2.48E-04	3.5			
	4-cell-embryo2-C4	4.60E-04	6.6			
	4-cell-embryo3-C1	3.28E-04	4.7			
	4-cell-embryo3-C2	6.34E-04	9.1			
	4-cell-embryo3-C3	3.72E-04	5.3			
	4-cell-embryo3-C4	4.98E-04	7.1			
	ESCp0-1-C1	4.96E-04	7.1	5.2E-04		
	ESCp0-1-C2	5.54E-04	7.9			
Human ES cells and cancer cells (Ref: Ramsköld et. al. 2012)	ESC1	3.47E-04	5.0	3.3E-04		
	ESC2	3.33E-04	4.8			
	ESC3	2.58E-04	3.7			
	ESC4	3.66E-04	5.2			
	ESC5	2.79E-04	4.0			
	ESC6	3.52E-04	5.0			
	ESC7	2.50E-04	3.6			
	ESC8	4.77E-04	6.8			
	SKMEL5 cell1	8.84E-04	12.6	7.0E-04		
	SKMEL5 cell2	7.77E-04	11.1			
	SKMEL5 cell3	6.30E-04	9.0			
	SKMEL5 cell4	9.47E-04	13.5			
	UACC257 cell1	5.42E-04	7.7			
	UACC257 cell2	5.11E-04	7.3			
	UACC257 cell3	6.10E-04	8.7			

Table S7: SNV validation using pyrosequencing. Related to Figure 3.

Locus	Cells	HiSeq variant calls	Pyrosequencing results
chr17:33478229	DT-cell #4 DT-cell #9B.1 DT-cell #9B.2	A-to-T	A-to-T
chr3:170078232	DT-cell #1 DT-cell #2 DT-cell #3 DT-cell #9B.2	G-to-A	G-to-A
chr17:6917703	DT-cell #1 DT-cell #2 DT-cell #9B.2	G-to-A	G-to-A
chr10:27459670	DT-cell #1 DT-cell #9B.1	C-to-T	C-to-T
chr13:76378459	S-cell #1 S-cell #2 DT-cell #3.1	T-to-C	T-to-C
chr16:2815237	DT-cell #2 DT-cell #4 DT-cell #9B.2	T-to-G	T-to-G
chr3:196612295	DT-cell #1 DT-cell #9B.1	G-to-T	G-to-T
chr3:196769982	S-cell #1 S-cell #2 S-cell #3 DT-cell #3.1	G-to-C	G-to-C
chr16:33963248	UNT-cell #4 UNT-cell #5 UNT-cell #6	T-to-C	T-to-C
chr9:33625096	UNT-cell #3 UNT-cell #6	T-to-C	T-to-C

The variant calls are made by using the Allele Quantification (AQ) Pyrosequencing Assay in the PyroMark Q24 1.010 software.

Table S8. RNA variants found in at least three out of five drug-tolerant single cells that were not present in untreated or stressed single cells. Related to Figure 3.

Locus	Gene affected	Mutation type
chr1:54232975	*TMEM48*	3'-UTR
chr1:54269670	*TMEM48*	Missense
chr2:128744486	*SAP130*	Missense
chr2:141816502	*LRP1B*	Missense
chr2:166626700	*GALNT3*	Missense
chr2:173916571	*RAPGEF4*	Missense
chr2:55201845	*RTN4*	Missense
chr2:55200973	*RTN4*	Missense
chr2:55200710	*RTN4*	Missense
chr3:45007193	*ZDHHC3*	Intron
chr3:63601583	*SYNPR*	3'-UTR
chr3:185211018	*ZDHHC3*	Missense
chr4:27010057	*STIM2*	Misense
chr5:139908435	*ANKHD1*	Missense
chr6:7882933	*MUTED / TXNDC5*	Missense / Silent
chr6:8015778	*MUTED / TXNDC5*	Missense / Silent
chr6:76412735	*SENP6*	Missense
chr6:122734789	*HSF2*	Missense
chr7:44425714	*NUDCD3*	Missense
chr7:93592725	*BET1*	3'-UTR
chr7:115894125	*TES*	Intron
chr7:138822678	*TTC26*	Missense
chr8:17885150	*PCM1*	Missense
chr9:95068105	*NOL8*	Missense
chr9:95072953	*NOL8*	Misense
chr9:123555243	*FBXW2*	Missense
chr10:12199974	*SEC61A2*	Missense
chr10:71977528	*PPA1*	Intron
chr11:83182669	*DLG2*	Missense
chr11:94607183	*AMOTL1*	3'-UTR
chr12:27542113	*ARNTL2*	Missense
chr12:42792740	*PPHLN1*	Stop Lost
chr12:69743928	*LYZ*	Silent
chr13:21044267	*CRYL1*	Intron
chr15:89021827	*MRPS11*	3'-UTR
chr17:64208161	*APOH*	3'-UTR
chr:19:46253959	AC074212.3	Silent
chr22:25592835	*KIAA1671*	3'-UTR

There are 38 novel RNA variants that are unique to the drug-tolerant single cells and are not present in dbSNP.

Table S9. Average depth of read coverage of genes associated with Paclitaxel-resistance

UNTREATED CELLS					
GENES	**UNT_1**	**UNT_2**	**UNT_3**	**UNT_4**	**UNT_5**
RAPGEF4	117	94	7	16	52
ABCC2	2	5	2	16	1
TOP2A	60	59	154	9	275
BCL2	0	1	0	0	10
TUBB4	9	401	0	11	56
BAX	69	1	0	1	57
BCL2L1	1244	19	0	15	42
TOP2B	12	145	50	27	41
ABCG2	2	2	1	3	2
TUBB2C	379	334	261	635	675
RB1	1	11	1	28	2
TUBB3	14	3	0	19	33
TP53	2	1	0	1	4
TOP1	15	22	2	1	8
TUBB2A	10	6	0	11	50
EGFR	1	77	1	7	20
MED12	2	6	5	78	2
STRESSED CELLS					
GENES	**S_1**	**S_2**	**S_3**	**S_4**	**S_5**
RAPGEF	19	60	6	39	95
ABCC2	1	2	17	1	1
TOP2A	43	1	56	11	40
BCL2	2	2	14	0	1
TUBB4	26	16	8	8	66
BAX	10	22	13	2	1426
BCL2L1	21	83	52	1	110
TOP2B	26	37	14	1	67
ABCG2	6	1	1	1	1
TUBB2C	353	411	126	333	467
RB1	4	1	2	2	1
TUBB3	24	19	8	26	81
TP53	4	7	1	17	2
TOP1	10	15	17	8	81
TUBB2A	69	236	11	19	52
EGFR	17	21	14	1	127
MED12	16	26	4	7	256
DRUG-TOLERANT CELLS					
GENES	**DT_1**	**DT_2**	**DT_3**	**DT_4**	**DT_5**
RAPGEF4	60	58	102	75	31
ABCC2	2	2	1	1	1
TOP2A	258	221	110	941	258
BCL2	0	0	0	0	0
TUBB4	3	29	32	32	2
BAX	2	6	1	1	82
BCL2L1	16	38	4	44	3
TOP2B	32	65	22	603	157
ABCG2	1	0	1	1	1
TUBB2C	400	1008	1244	1592	250
RB1	10	14	35	152	20
TUBB3	272	25	0	42	2
TP53	3	4	2	8	1
TOP1	30	161	33	25	3
TUBB2A	4	36	36	100	5
EGFR	129	1	1	925	62
MED12	1	4	1	127	10

Table S10: SNV in genes associated with Paclitaxel-resistance.

	Untreated cells	Stressed cells	Drug-tolerant cells
RAPGEF4	-	-	DT_1 (chr2: 173916571) missense DT_2 DT_5
ABCC2	-	-	-
TOP2A	UNT_5 (chr7:38572727) missense	S_1 (chr7:38548572) missense S_1 (cht7:38556634) missense	DT_1 (chr7: 38569794) missense
BCL2	-	-	-
TUBB4	-	-	-
BAX			DT_5 (chr19:49459472) missense
BCL2L1	-	-	-
TOP2B	-	-	-
ABCG2	-	-	-
TUBB2C	-	S_2 (chr9:140137975) missense	-
RB1	-	-	-
TUBB3	-	-	-
TP53	-	-	-
TOP1	-	-	DT_4 (chr20:9752843) 3'UTR
TUBB2A	-	-	-
EGFR	-	-	DT_5 (chr7:55274798) 3'UTR
MED12	-	-	-