

SI Appendix

Rapid emergence and mechanisms of resistance by U87 glioblastoma cells to doxorubicin in an in vitro tumor microfluidic ecology

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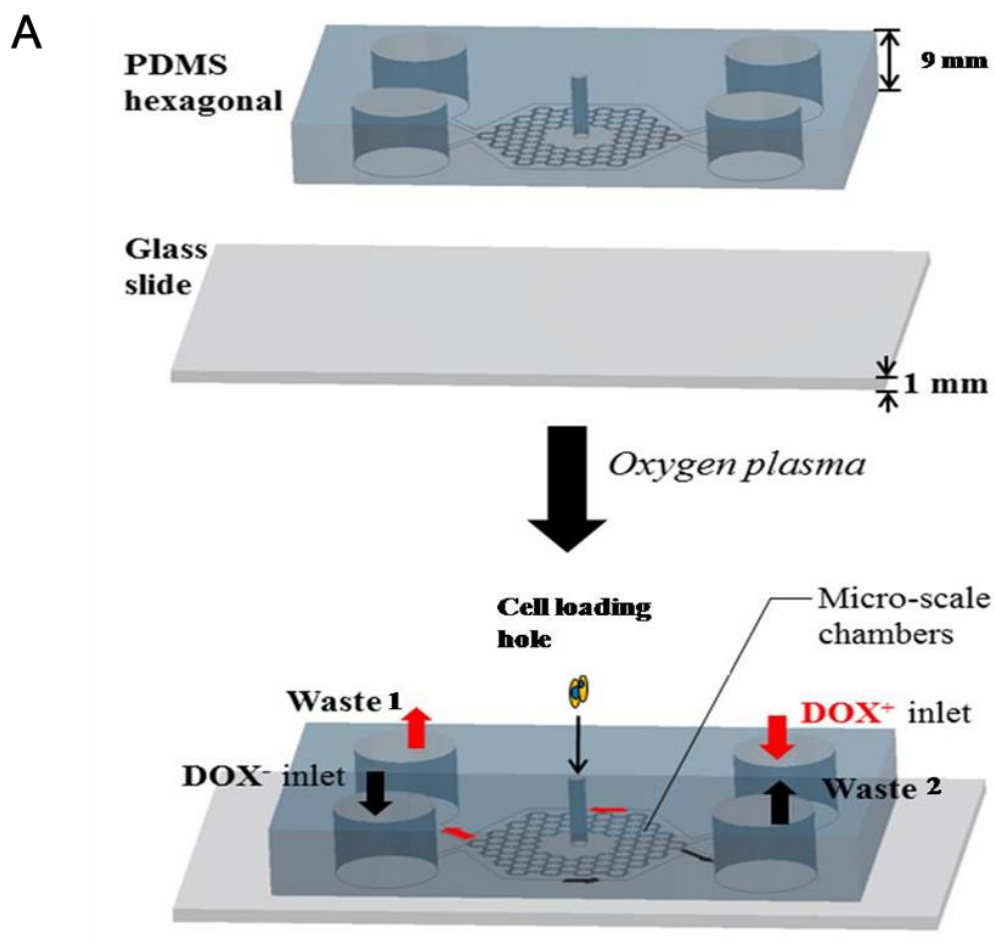
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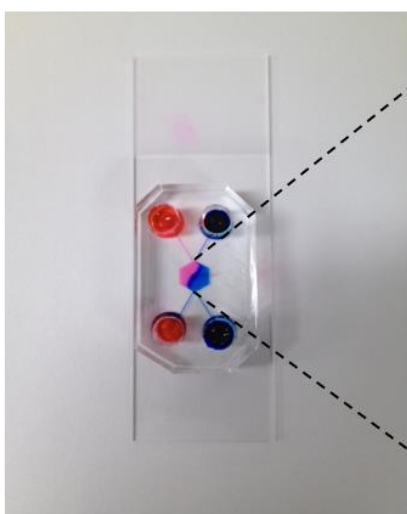
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Fig. S1. Structure and concentration gradient of the chip. Schematic figures show assembly and operation of a chip (A). Concentration gradient using red and blue ink shows the actual entire (B) and enlarged images (C).



B



C

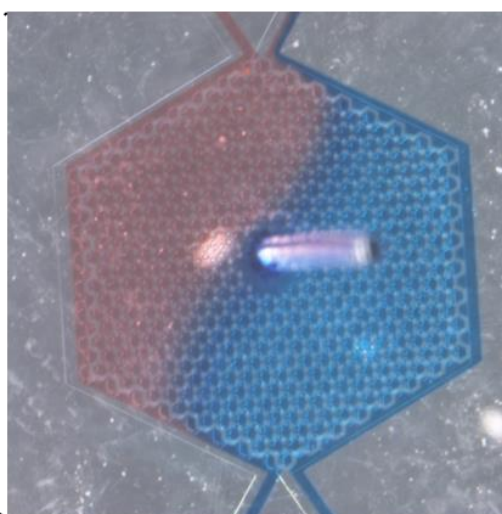
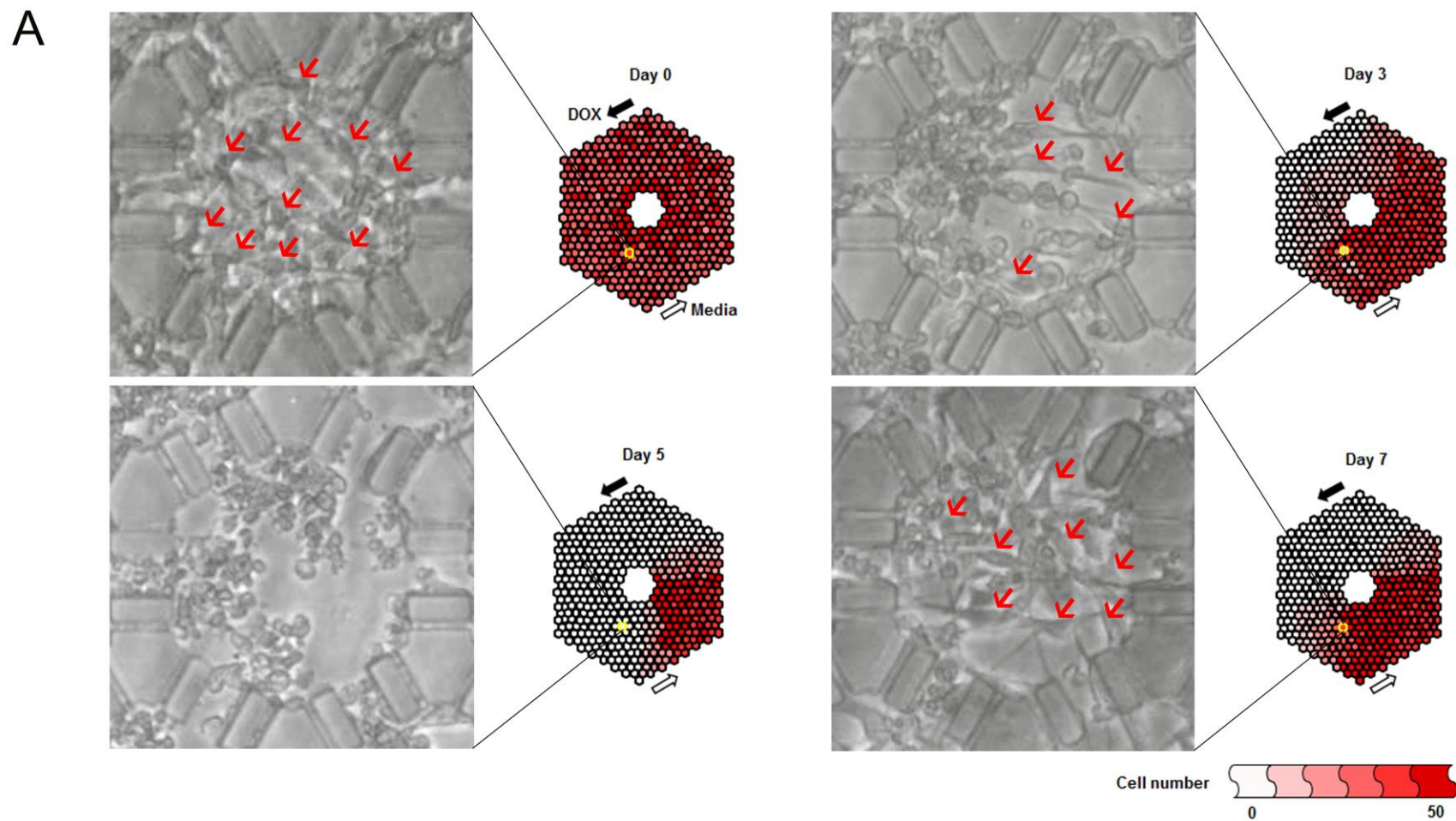
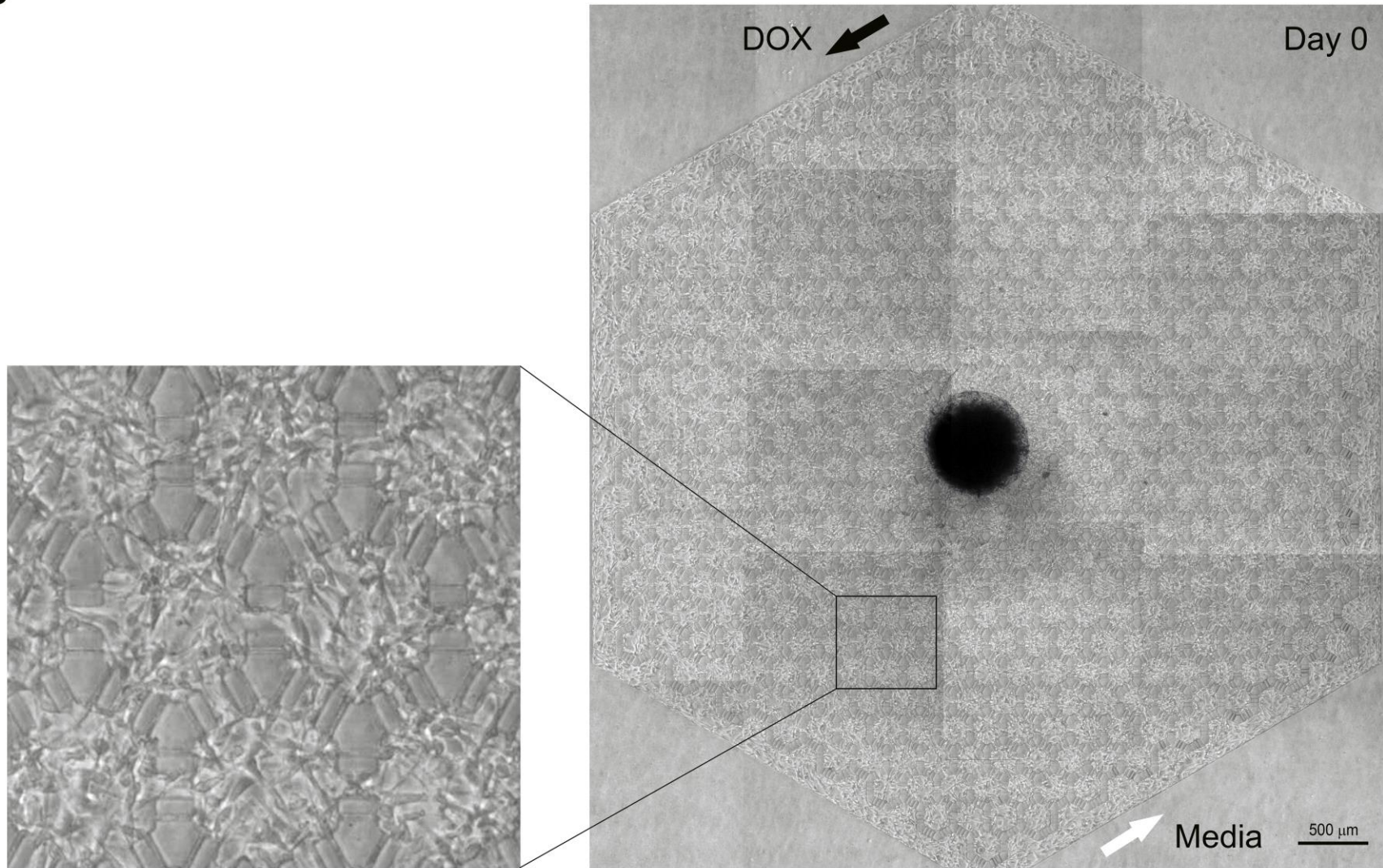


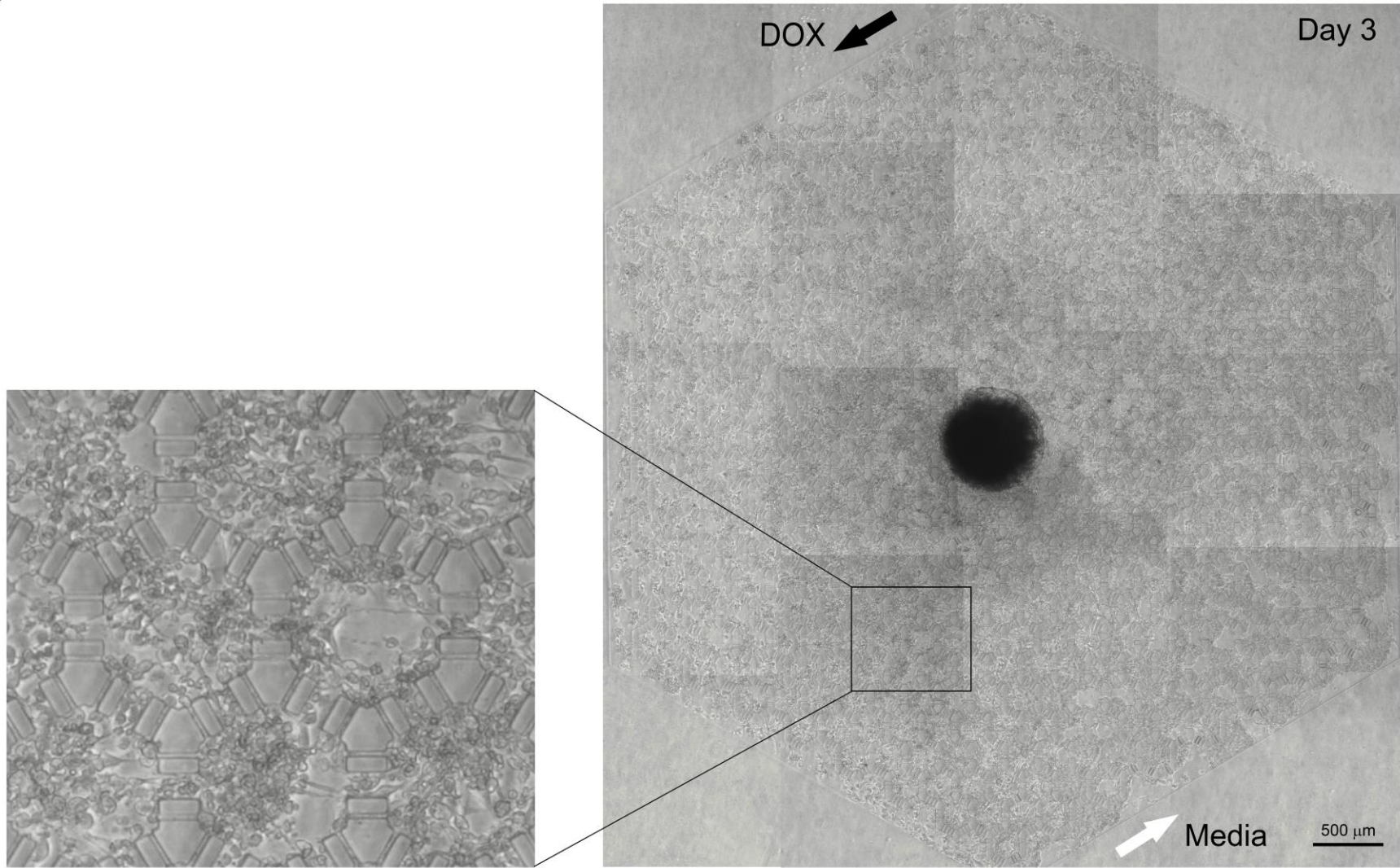
Fig. S2. Distribution of viable cells in the chip over a period of 7 days. (A) Enlarged pictures of viable cells. Polarized cells (red arrows) were counted as healthy cells in each chamber. (B-E) Microscope images of DOX-treated U87 cells on the chip on 0, 3, 5, and 7 days. Twenty images covering each part of the chip were stitched manually for each picture. Cells were observed under an inverted microscope (Magnification = 40 ×) (Eclipse TE 2000-U, Nikon) with a CCD camera (Progress C10 plus, Jenoptik AG, Jena, Germany).



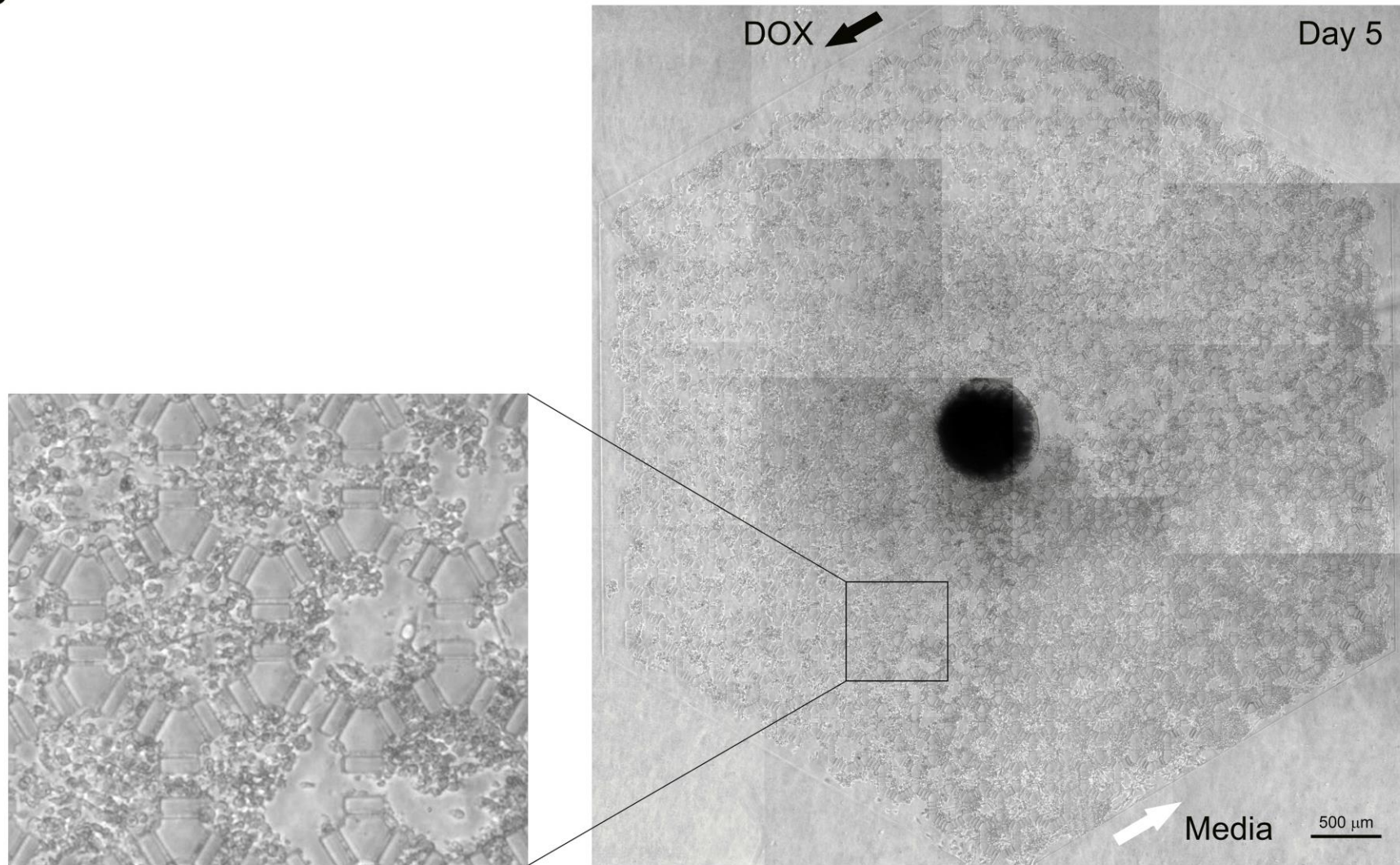
B



C



D



E

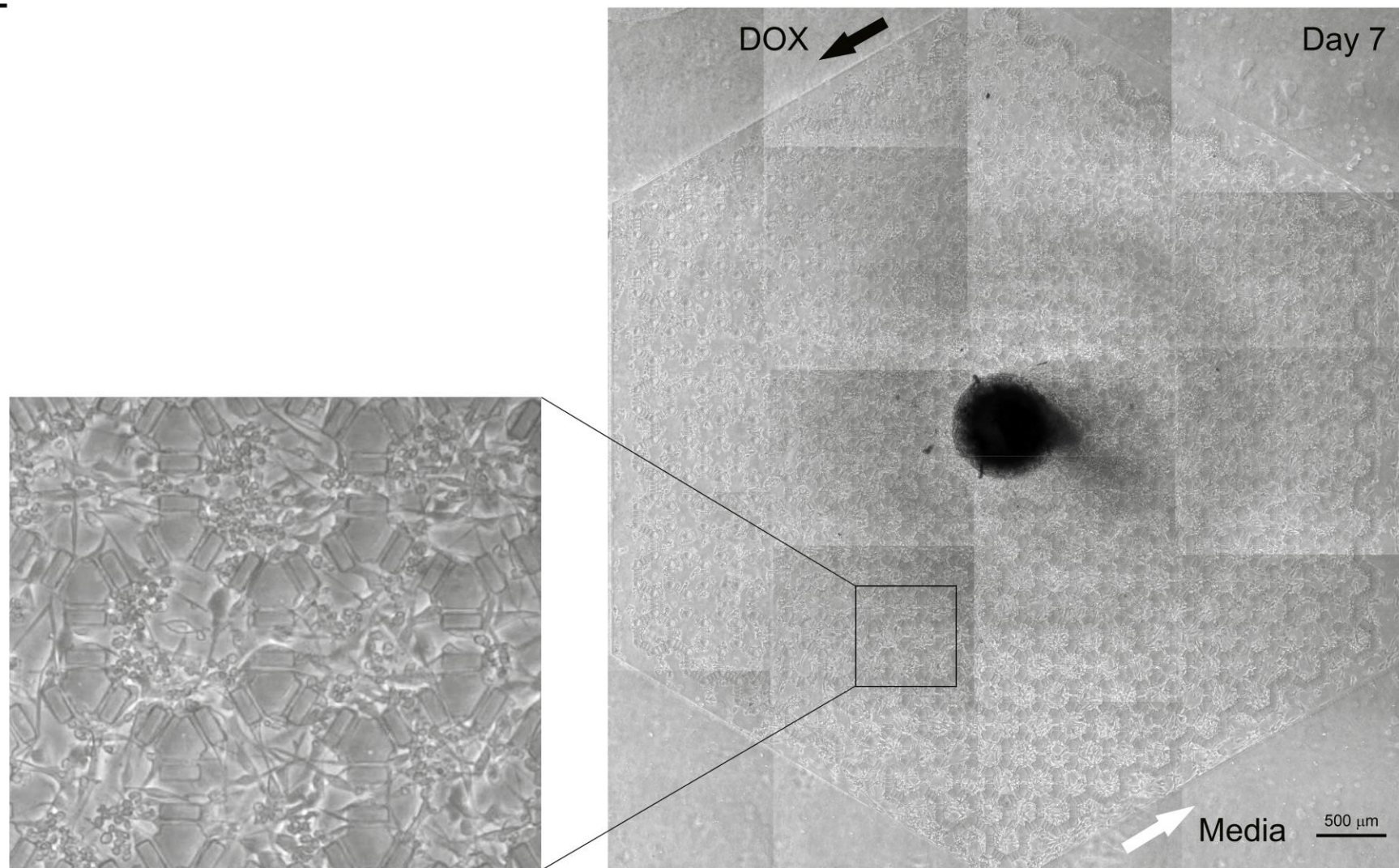


Fig. S3. siRNA knockdown of the *FLNA*, *CARD6* and *NSD1* in U87 cells. Relative mRNA levels for *FLNA* (A), *CARD6* (B) and *NSD1* (C) in U87 cells after a 48 hr-treatment with negative control (NC) or specific siRNAs (20 nM). Targeting sequences for the three genes are described in Materials and Methods. Bars indicate relative mRNA levels determined by real-time PCR analysis. * $P < 0.05$ with one-tailed t test.

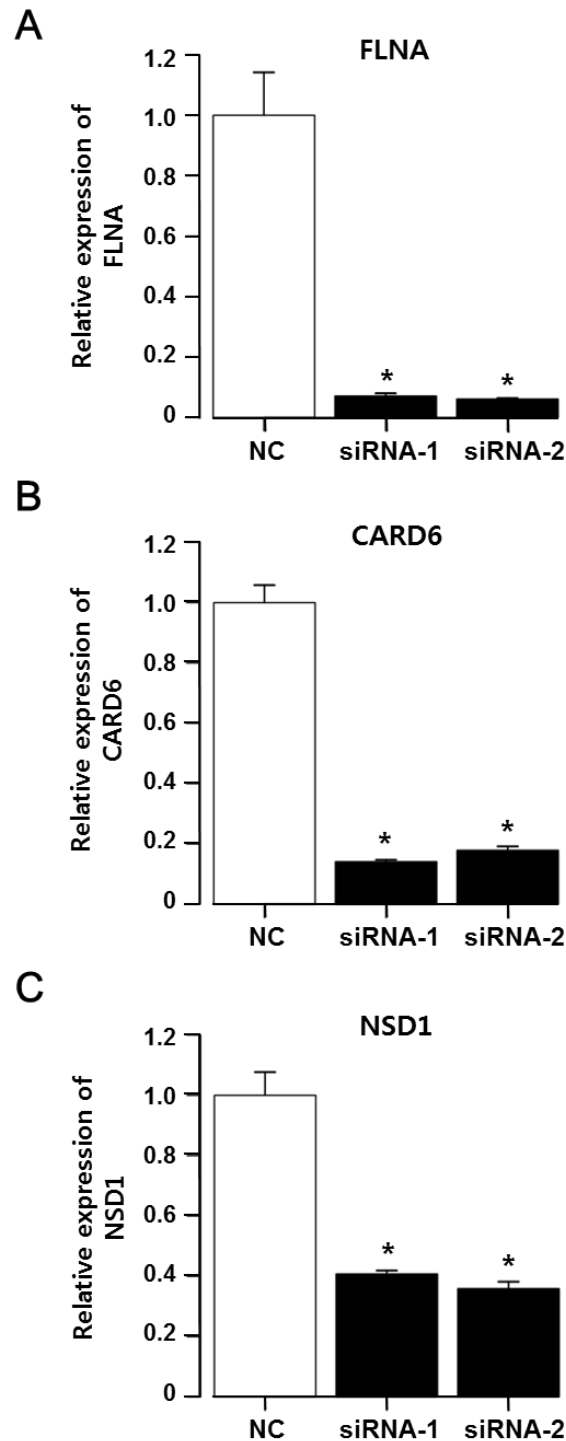


Table S1. List of mutations identified in resistant cells.

Gene name	Variant position	Ref allele	Alt allele	Variant type	# Programs	MuTect	Strelka	VarScan2	Virimid	U87-WT ref allele count	U87-WT alt allele count	U87-DR ref allele count	U87-DR alt allele count	U87-WT variant frequency	U87-DR variant frequency
FLNA	chrX:153580779	C	CT	frameshift substitution	2	-	O	O	-	124	1	79	46	0.01	0.37
CCDC33	chr15:74573138	T	TCATG GTGAG	nonframeshift substitution	2	-	O	O	-	26	0	22	13	0.00	0.37
CARD6	chr5:40853448	G	T	stopgain SNV	4	O	O	O	O	144	0	102	35	0.00	0.26
GOT1L1	chr8:37795200	C	T	stopgain SNV	4	O	O	O	O	105	0	83	23	0.00	0.22
LINGO1	chr15:77908136	G	T	stopgain SNV	3	O	O	X	O	58	0	42	10	0.00	0.19
C8orf34	chr8:69445270	A	T	stopgain SNV	3	O	O	X	O	79	0	73	12	0.00	0.14
ZNF850	chr19:37241539	C	A	stopgain SNV	3	O	O	X	O	166	0	148	25	0.00	0.14
ARSF	chrX:3019199	G	A	nonsynonymous SNV	4	O	O	O	O	29	0	11	20	0.00	0.65
DHX33	chr17:5364351	C	T	nonsynonymous SNV	4	O	O	O	O	24	0	24	23	0.00	0.49
NSD1	chr5:176638780	T	G	nonsynonymous SNV	4	O	O	O	O	80	1	70	37	0.01	0.35
LIPG	chr18:47101781	A	G	nonsynonymous SNV	4	O	O	O	O	63	0	28	13	0.00	0.32
SKOR2	chr18:44771284	C	G	nonsynonymous SNV	4	O	O	O	O	188	0	91	42	0.00	0.32
CHD1	chr5:98238646	G	A	nonsynonymous SNV	4	O	O	O	O	53	0	31	14	0.00	0.31
ERMARD	chr6:170179366	G	A	nonsynonymous SNV	4	O	O	O	O	57	0	60	25	0.00	0.29
RABGAP1	chr9:125852567	G	A	nonsynonymous SNV	4	O	O	O	O	192	0	119	48	0.00	0.29
SSH2	chr17:28022500	G	A	nonsynonymous SNV	4	O	O	O	O	156	0	139	58	0.00	0.29
ZXDC	chr3:126160744	C	G	nonsynonymous SNV	4	O	O	O	O	51	1	43	16	0.02	0.27
NLRP13	chr19:56424116	A	T	nonsynonymous SNV	4	O	O	O	O	138	0	108	39	0.00	0.27

TEP1	chr14:20852650	C	T	nonsynonymous SNV	4	O	O	O	O	136	0	139	48	0.00	0.26
TAAR8	chr6:132874459	C	T	nonsynonymous SNV	4	O	O	O	O	137	0	108	33	0.00	0.23
SLC16A9	chr10:61432626	A	T	nonsynonymous SNV	4	O	O	O	O	75	0	65	21	0.00	0.24
G3BP1	chr5:151179487	C	A	nonsynonymous SNV	4	O	O	O	O	50	0	44	13	0.00	0.23
NME9	chr3:138037054	G	T	nonsynonymous SNV	4	O	O	O	O	152	1	126	37	0.01	0.23
GAS8	chr16:90109746	C	T	nonsynonymous SNV	4	O	O	O	O	87	1	69	20	0.01	0.22
APOB	chr2:21228513	C	A	nonsynonymous SNV	4	O	O	O	O	184	0	137	39	0.00	0.22
KLHL6	chr3:183217557	A	C	nonsynonymous SNV	4	O	O	O	O	105	0	62	17	0.00	0.22
RPS6KA2	chr6:166844082	C	G	nonsynonymous SNV	4	O	O	O	O	138	0	112	29	0.00	0.21
ZNF570	chr19:37975635	G	T	nonsynonymous SNV	4	O	O	O	O	125	1	118	31	0.01	0.21
C8orf34	chr8:69552737	G	A	nonsynonymous SNV	4	O	O	O	O	51	0	44	11	0.00	0.20
ZNF41	chrX:47306866	A	G	nonsynonymous SNV	3	X	O	O	O	114	3	44	61	0.03	0.58
APOOL	chrX:84342596	G	T	nonsynonymous SNV	3	X	O	O	O	51	2	28	32	0.04	0.53
FMN1	chr15:33261185	G	A	nonsynonymous SNV	3	X	O	O	O	15	0	13	6	0.00	0.32
ADORA1	chr1:203134621	C	G	nonsynonymous SNV	3	X	O	O	O	318	2	282	95	0.01	0.25
FREM2	chr13:39425959	G	T	nonsynonymous SNV	3	O	O	X	O	101	0	82	21	0.00	0.20
FRMPD2	chr10:49440275	C	T	nonsynonymous SNV	3	O	O	O	X	41	1	39	10	0.02	0.20
SLC22A5	chr5:131724658	G	C	nonsynonymous SNV	3	O	O	O	X	57	1	54	14	0.02	0.21
LILRB1	chr19:55144739	C	T	nonsynonymous SNV	3	O	O	X	O	42	0	25	6	0.00	0.19
ERVV-1	chr19:53518647	A	G	nonsynonymous SNV	3	O	O	X	O	228	0	200	50	0.00	0.20
DLEC1	chr3:38163847	C	T	nonsynonymous SNV	3	O	O	X	O	112	1	82	19	0.01	0.19

TRMT1	chr19:13220389	C	G	nonsynonymous SNV	3	O	O	X	O	49	0	35	8	0.00	0.19
APOB	chr2:21231675	G	A	nonsynonymous SNV	3	O	O	X	O	99	0	94	21	0.00	0.18
RREB1	chr6:7231881	G	C	nonsynonymous SNV	3	O	O	X	O	21	0	31	6	0.00	0.16
C10orf71	chr10:50532588	C	G	nonsynonymous SNV	3	O	O	X	O	54	0	48	10	0.00	0.17
SLC10A7	chr4:147425023	G	A	nonsynonymous SNV	3	O	O	X	O	101	0	102	19	0.00	0.16
ZFAND4	chr10:46111895	G	A	nonsynonymous SNV	3	O	O	X	O	269	0	251	48	0.00	0.16
ARHGAP22	chr10:49658842	C	G	nonsynonymous SNV	3	O	O	X	O	30	0	40	7	0.00	0.15
CLK4	chr5:178040567	T	C	nonsynonymous SNV	3	O	O	X	O	27	0	30	5	0.00	0.14
C10orf71	chr10:50531137	A	T	nonsynonymous SNV	3	O	O	X	O	94	1	116	19	0.01	0.14
FRMPD2	chr10:49420008	T	C	nonsynonymous SNV	3	O	O	X	O	43	0	44	7	0.00	0.14
CHIT1	chr1:203192351	A	G	nonsynonymous SNV	3	O	O	X	O	44	0	36	6	0.00	0.14
URI1	chr19:30505869	G	A	nonsynonymous SNV	3	O	O	X	O	147	0	118	14	0.00	0.11
COQ9	chr16:57486804	C	T	nonsynonymous SNV	3	O	O	X	O	22	0	28	3	0.00	0.10
GPRIN2	chr10:46999577	G	T	nonsynonymous SNV	3	O	O	X	O	102	0	149	18	0.00	0.11
MLLT4	chr6:168348550	G	A	nonsynonymous SNV	3	O	O	X	O	76	0	59	6	0.00	0.09
CCL21	chr9:34709668	C	T	nonsynonymous SNV	3	O	O	X	O	76	0	65	6	0.00	0.08
NIN	chr14:51224525	C	T	nonsynonymous SNV	3	O	O	X	O	253	0	247	19	0.00	0.07
SCYL1	chr11:65298230	G	A	nonsynonymous SNV	3	O	O	X	O	83	0	62	5	0.00	0.07
C3orf58	chr3:143704664	G	A	nonsynonymous SNV	3	O	O	X	O	124	0	144	10	0.00	0.06
LAMA1	chr18:6997823	A	G	nonsynonymous SNV	2	X	O	X	O	13	0	16	4	0.00	0.20
SUSD5	chr3:33195250	G	A	nonsynonymous SNV	2	X	O	X	O	200	2	197	46	0.01	0.19

IGSF21	chr1:18661463	A	T	nonsynonymous SNV	2	X	O	X	O	160	2	161	38	0.01	0.19
GPRIN2	chr10:46999596	G	A	nonsynonymous SNV	2	X	O	O	X	70	0	88	16	0.00	0.15
C10orf71	chr10:50532812	A	G	nonsynonymous SNV	2	O	O	X	X	195	1	221	38	0.01	0.15
C10orf71	chr10:50533463	T	A	nonsynonymous SNV	2	O	O	X	X	51	1	55	6	0.02	0.10
GPRIN2	chr10:46999484	G	T	nonsynonymous SNV	2	O	O	X	X	63	1	94	10	0.02	0.10
C10orf71	chr10:50534350	G	A	nonsynonymous SNV	2	O	O	X	X	28	0	46	5	0.00	0.10
C10orf71	chr10:50533841	G	C	nonsynonymous SNV	2	X	O	X	O	64	0	83	7	0.00	0.08
GPRIN2	chr10:46999863	C	G	nonsynonymous SNV	2	O	O	X	X	102	1	130	9	0.01	0.06
SERINC4	chr15:44087290	A	T	nonsynonymous SNV	2	O	O	X	X	63	0	52	4	0.00	0.07
OR2T6	chr1:248551225	G	T	nonsynonymous SNV	2	O	O	X	X	199	0	222	14	0.00	0.06
PDZRN4	chr12:41966862	C	T	nonsynonymous SNV	2	O	O	X	X	108	0	102	7	0.00	0.06
ITGAE	chr17:3660365	C	T	nonsynonymous SNV	2	O	O	X	X	136	1	162	7	0.01	0.04
ARMCX3	chrX:100880326	C	T	synonymous SNV	4	O	O	O	O	52	0	37	24	0.00	0.39
MYH13	chr17:10212617	C	T	synonymous SNV	4	O	O	O	O	24	0	23	12	0.00	0.34
ASB18	chr2:237103611	C	G	synonymous SNV	4	O	O	O	O	84	0	57	25	0.00	0.30
KIF13B	chr8:28928096	G	A	synonymous SNV	4	O	O	O	O	76	0	46	19	0.00	0.29
SAMD14	chr17:48195018	C	T	synonymous SNV	4	O	O	O	O	27	0	13	5	0.00	0.28
EHBP1	chr2:63272563	G	A	synonymous SNV	4	O	O	O	O	145	0	110	41	0.00	0.27
KLHDC7A	chr1:18808805	A	C	synonymous SNV	4	O	O	O	O	107	0	71	26	0.00	0.27
FAM84A	chr2:14774538	C	T	synonymous SNV	4	O	O	O	O	31	0	18	6	0.00	0.25
KLF7	chr2:207988993	G	A	synonymous SNV	4	O	O	O	O	116	1	104	32	0.01	0.24

FBLN2	chr3:13611975	G	A	synonymous SNV	4	O	O	O	O	35	0	16	5	0.00	0.24
WNT3A	chr1:228246737	C	G	synonymous SNV	4	O	O	O	O	90	0	63	17	0.00	0.21
DCAF10	chr9:37861377	C	T	synonymous SNV	4	O	O	O	O	111	0	91	25	0.00	0.22
PIGL	chr17:16137346	G	A	synonymous SNV	4	O	O	O	O	48	0	33	9	0.00	0.21
RXFP4	chr1:155912253	G	T	synonymous SNV	4	O	O	O	O	96	0	59	16	0.00	0.21
CLDN18	chr3:137742517	C	A	synonymous SNV	4	O	O	O	O	38	0	32	8	0.00	0.20
BAI2	chr1:32207763	G	A	synonymous SNV	3	O	O	O	X	29	0	9	3	0.00	0.25
PHF13	chr1:6681583	C	T	synonymous SNV	3	O	O	X	O	186	0	130	28	0.00	0.18
SLC25A27	chr6:46637908	A	C	synonymous SNV	3	O	O	X	O	71	0	69	14	0.00	0.17
PANK4	chr1:2451376	C	T	synonymous SNV	3	O	O	X	O	40	0	25	5	0.00	0.17
SREBF2	chr22:42269831	G	A	synonymous SNV	3	O	O	X	O	52	0	39	8	0.00	0.17
CXCL12	chr10:44873197	T	C	synonymous SNV	3	O	O	X	O	42	0	37	7	0.00	0.16
ZGPAT	chr20:62364958	C	T	synonymous SNV	3	O	O	X	O	179	1	155	32	0.01	0.17
FRMPD2	chr10:49420066	A	G	synonymous SNV	3	O	O	X	O	62	0	65	13	0.00	0.17
ESPL1	chr12:53666593	C	T	synonymous SNV	3	O	O	X	O	53	0	56	11	0.00	0.16
SYCP2	chr20:58457012	G	T	synonymous SNV	3	O	O	X	O	62	0	52	9	0.00	0.15
C10orf10	chr10:45473317	C	T	synonymous SNV	3	O	O	X	O	118	0	118	23	0.00	0.16
CAGE1	chr6:7378979	A	C	synonymous SNV	3	O	O	X	O	26	0	52	9	0.00	0.15
ATP6V1B2	chr8:20075750	C	T	synonymous SNV	3	O	O	X	O	83	0	55	9	0.00	0.14
TRIP10	chr19:6749948	A	G	synonymous SNV	3	O	O	X	O	87	0	70	10	0.00	0.13
GALR2	chr17:74073314	G	A	synonymous SNV	3	O	O	X	O	106	0	82	12	0.00	0.13

ZNF543	chr19:57835121	G	A	synonymous SNV	3	O	O	X	O	142	1	117	15	0.01	0.11
ANKRD30A	chr10:37508234	C	T	synonymous SNV	3	O	O	X	O	137	0	124	17	0.00	0.12
GPRIN2	chr10:46999732	G	A	synonymous SNV	3	O	O	X	O	177	0	215	29	0.00	0.12
SDSL	chr12:113875794	C	T	synonymous SNV	3	O	O	X	O	89	0	48	6	0.00	0.11
FRA10AC1	chr10:95452426	C	T	synonymous SNV	3	O	O	X	O	129	0	98	13	0.00	0.12
DCAF6	chr1:168034905	G	A	synonymous SNV	3	O	O	X	O	18	0	30	3	0.00	0.09
VPS8	chr3:184689525	C	T	synonymous SNV	3	O	O	X	O	160	0	145	12	0.00	0.08
UACA	chr15:70961088	C	T	synonymous SNV	3	O	O	X	O	108	0	92	6	0.00	0.06
LRRN1	chr3:3887876	T	C	synonymous SNV	2	X	O	O	X	92	4	107	71	0.04	0.40
GPRIN2	chr10:47000071	G	A	synonymous SNV	2	X	O	X	O	12	0	16	5	0.00	0.24
TUBGCP4	chr15:43692294	C	T	synonymous SNV	2	X	O	O	X	178	4	133	34	0.02	0.20
C10orf71	chr10:50533617	T	C	synonymous SNV	2	O	O	X	X	134	1	143	19	0.01	0.12
ZNF594	chr17:5085959	G	A	synonymous SNV	2	O	O	X	X	74	1	62	7	0.01	0.10
MUC6	chr11:1017056	A	G	synonymous SNV	2	X	O	X	O	212	1	254	32	0.00	0.11
FAM13C	chr10:61043136	C	A	synonymous SNV	2	X	O	X	O	39	0	44	4	0.00	0.08
DSP	chr6:7584260	G	A	synonymous SNV	2	O	O	X	X	84	0	134	8	0.00	0.06
ADAMTS20	chr12:43833754	G	A	synonymous SNV	2	O	O	X	X	89	0	95	6	0.00	0.06
LRTOMT	chr11:71806443	C	T	synonymous SNV	2	O	O	X	X	123	0	123	6	0.00	0.05
ANK2	chr4:114279242	C	T	synonymous SNV	2	O	O	X	X	125	0	109	6	0.00	0.05
NDUFS6	chr5:1814491	G	A	synonymous SNV	2	O	O	X	X	193	0	187	10	0.00	0.05

Table S2. Gene Ontology enrichment analysis for mutated genes.

(A) GO Biological Process

Term		Count	Genes	P-value
GO:0065007	biological regulation	38	SSH2, KLHL6, ARHGAP22, SCYL1, ZNF41, LILRB1, LIPG, ZNF570, NME9, APOB, LAMA1, CHD1, GAS8, LINGO1, RPS6KA2, ADORA1, DHX33, RABGAP1, CLK4, CCL21, URI1, SLC22A5, CARD6, DLEC1, ZXDC, RREB1, FMN1, TEP1, FLNA, ZNF850, NIN, MLLT4, NSD1, ITGAE, C8orf34, TAAR8, G3BP1, SKOR2	0.0028
GO:0015837	amine transport	3	LILRB1, ADORA1, SLC22A5	0.0033
GO:0008064	regulation of actin polymerization or depolymerization	3	CCL21, SSH2, FMN1	0.0036
GO:0050794	regulation of cellular process	35	SSH2, KLHL6, ARHGAP22, SCYL1, ZNF41, LILRB1, LIPG, ZNF570, NME9, APOB, LAMA1, CHD1, GAS8, LINGO1, RPS6KA2, ADORA1, DHX33, RABGAP1, CLK4, CCL21, URI1, CARD6, DLEC1, ZXDC, RREB1, FMN1, FLNA, ZNF850, MLLT4, NSD1, ITGAE, C8orf34, TAAR8, SKOR2, G3BP1	0.0037
GO:0030832	regulation of actin filament length	3	CCL21, SSH2, FMN1	0.0038
GO:0050789	regulation of biological process	36	SSH2, KLHL6, ARHGAP22, SCYL1, ZNF41, LILRB1, LIPG, ZNF570, NME9, APOB, LAMA1, CHD1, GAS8, LINGO1, RPS6KA2, ADORA1, DHX33, RABGAP1, CLK4, CCL21, URI1, SLC22A5, CARD6, DLEC1, ZXDC, RREB1, FMN1, FLNA, ZNF850, MLLT4, NSD1, ITGAE, C8orf34, TAAR8, G3BP1, SKOR2	0.0048
GO:0007015	actin filament organization	4	CCL21, SSH2, FLNA, FMN1	0.0053
GO:0008154	actin polymerization or depolymerization	3	CCL21, SSH2, FMN1	0.0072
GO:0006898	receptor-mediated endocytosis	3	CCL21, LILRB1, APOB	0.0096
GO:0097285	cell-type specific apoptotic process	4	CCL21, LILRB1, RPS6KA2, ADORA1	0.0108
GO:0090066	regulation of anatomical structure size	4	CCL21, SSH2, ADORA1, FMN1	0.0134
GO:0034329	cell junction assembly	3	MLLT4, FRMPD2, FLNA	0.0189
GO:0032956	regulation of actin cytoskeleton organization	3	CCL21, SSH2, FMN1	0.0195

GO:0032535	regulation of cellular component size	3	CCL21, SSH2, FMN1	0.0198
GO:0030001	metal ion transport	5	CCL21, LILRB1, ADORA1, SLC10A7, SLC22A5	0.0241
GO:0032970	regulation of actin filament-based process	3	CCL21, SSH2, FMN1	0.0256
GO:0080090	regulation of primary metabolic process	21	RREB1, ZXDC, ARHGAP22, SCYL1, ZNF41, LILRB1, LIPG, FLNA, ZNF570, APOB, ZNF850, CHD1, NSD1, RPS6KA2, ADORA1, DHX33, RABGAP1, URI1, CCL21, CLK4, SKOR2	0.0267
GO:0034330	cell junction organization	3	MLLT4, FRMPD2, FLNA	0.0270
GO:0051235	maintenance of location	3	CCL21, FLNA, NIN	0.0299
GO:0030031	cell projection assembly	3	CCL21, SSH2, FLNA	0.0299
GO:0008285	negative regulation of cell proliferation	5	LILRB1, DLEC1, RPS6KA2, ADORA1, GAS8	0.0301
GO:0006897	endocytosis	4	CCL21, LILRB1, ADORA1, APOB	0.0314
GO:0010468	regulation of gene expression	17	NSD1, RPS6KA2, RREB1, ZXDC, DHX33, ARHGAP22, SCYL1, CLK4, CCL21, ZNF41, LILRB1, URI1, FLNA, ZNF570, SKOR2, ZNF850, CHD1	0.0343
GO:0019216	regulation of lipid metabolic process	3	CCL21, ADORA1, APOB	0.0358
GO:0019219	regulation of nucleobase-containing compound metabolic process	17	NSD1, RREB1, ZXDC, DHX33, RABGAP1, ARHGAP22, SCYL1, CLK4, CCL21, URI1, ZNF41, LILRB1, FLNA, ZNF570, SKOR2, ZNF850, CHD1	0.0399
GO:0030036	actin cytoskeleton organization	4	CCL21, SSH2, FLNA, FMN1	0.0459
GO:0002764	immune response-regulating signaling pathway	3	LILRB1, RPS6KA2, KLHL6	0.0479
GO:0051252	regulation of RNA metabolic process	15	NSD1, RREB1, ZXDC, DHX33, ARHGAP22, SCYL1, CLK4, ZNF41, LILRB1, URI1, FLNA, ZNF570, SKOR2, ZNF850, CHD1	0.0487
GO:0050900	leukocyte migration	3	CCL21, ADORA1, APOB	0.0493
GO:0051171	regulation of nitrogen compound metabolic process	17	NSD1, RREB1, ZXDC, DHX33, RABGAP1, ARHGAP22, SCYL1, CLK4, CCL21, URI1, ZNF41, LILRB1, FLNA, ZNF570, SKOR2, ZNF850, CHD1	0.0495
GO:0016311	dephosphorylation	3	URI1, SSH2, ADORA1	0.0498

(B) GO Molecular Function

	Term	Count	Genes	P-value
GO:0097367	carbohydrate derivative binding	4	LIPG, CHIT1, APOB, SUSD5	0.0033
GO:0070035	purine NTP-dependent helicase activity	3	G3BP1, DHX33, CHD1	0.0051
GO:0008026	ATP-dependent helicase activity	3	G3BP1, DHX33, CHD1	0.0051
GO:0043168	anion binding	15	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, LIPG, FRMPD2, NME9, G3BP1, GOT1L1, APOB, CHD1, NIN, SLC22A5	0.0070
GO:0015293	symporter activity	3	SLC16A9, SLC10A7, SLC22A5	0.0084
GO:0043167	ion binding	27	NLRP13, RREB1, ZXDC, SCYL1, TRMT1, TEP1, ZNF41, LIPG, FRMPD2, ZNF570, PDZRN4, NME9, ARSF, GOT1L1, APOB, ZNF850, CHD1, NIN, NSD1, RPS6KA2, DHX33, ZFAND4, FREM2, CLK4, CHIT1, G3BP1, SLC22A5	0.0119
GO:0001883	purine nucleoside binding	12	NLRP13, RPS6KA2, ADORA1, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, NIN, SLC22A5	0.0121
GO:0004386	helicase activity	3	G3BP1, DHX33, CHD1	0.0125
GO:0001882	nucleoside binding	12	NLRP13, RPS6KA2, ADORA1, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, NIN, SLC22A5	0.0127
GO:0005524	ATP binding	10	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, SLC22A5	0.0183
GO:0005539	glycosaminoglycan binding	3	LIPG, APOB, SUSD5	0.0192
GO:0032559	adenyl ribonucleotide binding	10	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, SLC22A5	0.0208
GO:0030554	adenyl nucleotide binding	10	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, SLC22A5	0.0212
GO:0003714	transcription corepressor activity	3	URH1, NSD1, SKOR2	0.0229
GO:0015291	secondary active transmembrane transporter activity	3	SLC16A9, SLC10A7, SLC22A5	0.0245
GO:0035639	purine ribonucleoside triphosphate binding	11	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, NIN, SLC22A5	0.0284
GO:0032550	purine ribonucleoside binding	11	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, NIN, SLC22A5	0.0293

GO:0032549	ribonucleoside binding	11	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, NIN, SLC22A5	0.0298
GO:0032555	purine ribonucleotide binding	11	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, NIN, SLC22A5	0.0322
GO:0017076	purine nucleotide binding	11	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, NIN, SLC22A5	0.0330
GO:0032553	ribonucleotide binding	11	NLRP13, RPS6KA2, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, CHD1, NIN, SLC22A5	0.0339
GO:0036094	small molecule binding	14	NLRP13, RPS6KA2, ADORA1, DHX33, SCYL1, TEP1, CLK4, NME9, G3BP1, SKOR2, GOT1L1, CHD1, NIN, SLC22A5	0.0348
GO:0005102	receptor binding	8	CCL21, LILRB1, NSD1, FLNA, ADORA1, APOB, LAMA1, LINGO1	0.0397

(C) GO Cellular Component

Term		Count	Genes	P-value
GO:0030662	coated vesicle membrane	3	APOB, C3orf58, SCYL1	0.0108
GO:0016323	basolateral plasma membrane	3	FRMPD2, ADORA1, SLC22A5	0.0144
GO:0005856	cytoskeleton	11	SSH2, RPS6KA2, ADORA1, FMN1, RABGAP1, SCYL1, FRMPD2, FLNA, NME9, NIN, GAS8	0.0172
GO:0030135	coated vesicle	3	APOB, C3orf58, SCYL1	0.0425
GO:0005576	extracellular region	11	IGSF21, FREM2, CCL21, LIPG, FLNA, CHIT1, ARSF, APOOL, LAMA1, APOB, C3orf58	0.0461

Table S3. List of differentially expressed genes. LogFC and logCPM (counts_per_million)

indicate the fold change and overall expression in log scale.

Genes	Expression		edgeR Results		
	U87-WT	U87-DR	logFC	logCPM	p-value
AKR1B1	9001.86	105056.35	3.54	12.40	3.53E-03
AKR1C1	388.21	8119.04	4.39	8.66	2.38E-03
AKR1C2	90.85	650.82	2.84	5.14	6.70E-03
AKR1C3	199.52	1146.81	2.52	6.00	7.05E-03
ALPK2	173.84	2289.61	3.72	6.87	3.18E-03
ANXA8L2	0.00	66.75	9.06	1.74	9.69E-03
ATF3	64.18	619.43	3.27	5.03	5.25E-03
ATP1B1	373.40	1732.90	2.21	6.64	9.64E-03
ATP5J2-PTCD1	89.96	0.03	-9.49	2.16	6.97E-03
BDKRB1	275.59	1385.70	2.33	6.30	8.32E-03
C11orf96	7.87	282.35	5.14	3.80	3.89E-03
C1orf151-NBL1	175.91	0.03	-10.46	3.10	3.55E-03
C3	235.09	4842.45	4.36	7.91	2.39E-03
CA9	3289.81	523.36	-2.65	7.50	6.03E-03
CCL2	48.37	916.01	4.24	5.52	2.64E-03
CHAC1	19.72	246.93	3.64	3.68	8.12E-03
COL5A3	86.90	549.59	2.66	4.92	8.70E-03
CRYAB	6.88	157.85	4.49	3.00	8.06E-03
CSF3	215.33	3395.98	3.98	7.42	2.78E-03
CXCL1	27.63	366.37	3.72	4.24	5.82E-03
CXCL2	60.23	492.91	3.03	4.72	6.81E-03
CXCL3	35.53	325.89	3.19	4.11	9.01E-03
ETS2	329.93	1777.43	2.43	6.65	7.53E-03
FAM156B	173.93	0.03	-10.44	3.08	3.59E-03
FBXO2	7.87	238.83	4.90	3.57	4.85E-03
FGF2	912.80	4372.79	2.26	7.97	8.86E-03
FILIP1L	256.82	1405.94	2.45	6.30	7.23E-03
FLJ43663	163.96	1433.27	3.13	6.25	4.21E-03
FLJ46300	0.96	204.41	7.52	3.31	3.44E-03
GDF15	277.57	2606.44	3.23	7.10	4.13E-03
GLS	1985.68	9169.76	2.21	9.05	9.95E-03

HIST2H2AA3	66.15	494.93	2.90	4.74	7.46E-03
HIST2H2BE	123.45	784.43	2.67	5.43	6.82E-03
HSPA6	18.74	3086.22	7.35	7.20	1.37E-03
IER3	817.96	5569.24	2.77	8.24	5.37E-03
IGFBP5	37.50	374.47	3.31	4.30	7.39E-03
IL11	150.13	970.68	2.69	5.74	6.33E-03
IL1B	367.47	1720.75	2.23	6.63	9.50E-03
IL6	130.37	2247.09	4.11	6.82	2.65E-03
IL8	205.45	4431.49	4.43	7.78	2.32E-03
INHBE	25.65	284.38	3.46	3.89	7.98E-03
INO80B-WBP1	94.90	0.03	-9.57	2.23	6.78E-03
KIAA1199	1322.78	9460.26	2.84	9.00	5.17E-03
KLF5	230.15	1096.20	2.25	5.98	9.38E-03
LOC645638	49.36	462.54	3.22	4.61	6.18E-03
LOXL4	30.59	311.71	3.34	4.04	8.35E-03
MMP3	181.74	1546.64	3.09	6.36	4.26E-03
MRGPRF	42.44	382.57	3.17	4.35	7.44E-03
MSC	168.90	875.54	2.37	5.64	8.96E-03
MSMO1	484.05	2318.98	2.26	7.06	9.40E-03
MYH15	236.08	1291.56	2.45	6.18	7.48E-03
MYZAP	75.05	523.27	2.80	4.84	7.90E-03
NADKD1	402.05	2592.27	2.69	7.15	5.98E-03
NBL1	0.00	201.37	10.66	3.28	3.25E-03
NUPR1	84.92	751.02	3.14	5.32	5.07E-03
NYAP1	2.93	119.39	5.27	2.58	8.37E-03
PI3	12.81	866.40	6.06	5.39	1.81E-03
PLAT	234.10	1379.62	2.56	6.26	6.57E-03
PRRG4	69.12	436.22	2.66	4.59	9.95E-03
PRSS35	4.91	475.68	6.55	4.52	2.08E-03
PTGS2	121.48	1360.38	3.48	6.14	3.54E-03
PTX3	879.21	4226.02	2.26	7.92	9.12E-03
RANBP3L	42.44	1808.79	5.41	6.46	1.71E-03
RCAN1	437.61	5790.91	3.73	8.21	3.08E-03
RGS16	0.00	140.64	10.14	2.77	4.56E-03
RN7SK	7.87	154.82	4.27	2.98	8.96E-03
RND3	1074.82	5038.84	2.23	8.18	9.31E-03

RPS17	667.90	0.03	-12.38	4.99	1.64E-03
RSPO3	50.35	601.21	3.57	4.96	4.40E-03
S100A9	7.87	422.04	5.72	4.36	2.61E-03
SAT1	327.95	2048.71	2.64	6.82	6.18E-03
SLC3A2	863.40	4307.00	2.32	7.94	8.51E-03
SLC5A3	1947.15	11954.40	2.62	9.36	6.34E-03
SLC6A12	10.83	1451.47	7.05	6.12	1.45E-03
SLC6A9	27.63	489.86	4.14	4.63	3.89E-03
SLPI	2.93	242.87	6.30	3.56	3.48E-03
SOD2	963.18	5009.49	2.38	8.15	7.75E-03
SULF2	23.67	347.14	3.87	4.15	5.65E-03
TNFSF15	7.87	341.06	5.41	4.06	3.19E-03
TNFSF9	159.02	1135.67	2.84	5.94	5.20E-03
TRIB3	84.92	610.33	2.84	5.05	6.93E-03
WISP1	65.17	587.04	3.17	4.96	5.70E-03
ZNF295-AS1	0.00	66.75	9.06	1.74	9.69E-03

Table S4. KEGG and Gene Ontology enrichment analysis for differentially expressed genes.

(A) KEGG pathway

	Term	Count	Genes	FDR
hsa04060	Cytokine-cytokine receptor interaction	12	CSF3, IL11, CCL2, IL6, CXCL3, IL8, INHBE, CXCL1, TNFSF15, CXCL2, IL1B, TNFSF9	2.46E-08
hsa04621	NOD-like receptor signaling pathway	6	CXCL1, CXCL2, IL1B, CCL2, IL6, IL8	1.33E-06
hsa05323	Rheumatoid arthritis	7	CXCL1, IL11, MMP3, IL1B, CCL2, IL6, IL8	1.33E-06
hsa05144	Malaria	5	CSF3, IL1B, CCL2, IL6, IL8	1.55E-05

(B) GO Biological Process

	Term	Count	Genes	FDR
GO:0010574	regulation of vascular endothelial growth factor production	6	C3, PTGS2, IL1B, CCL2, IL6, SULF2	3.31E-07
GO:0010573	vascular endothelial growth factor production	6	C3, PTGS2, IL1B, CCL2, IL6, SULF2	3.31E-07
GO:0009611	response to wounding	21	C3, IL11, SLC3A2, FGF2, CCL2, CXCL3, SOD2, CXCL2, ATP1B1, PLAT, IL1B, IER3, PTGS2, MMP3, NUPR1, IL6, PTX3, IL8, CXCL1, BDKRB1, S100A9	2.64E-06
GO:0030647	aminoglycoside antibiotic metabolic process	4	AKR1B1, AKR1C1, AKR1C2, AKR1C3	3.89E-06
GO:0044597	daunorubicin metabolic process	4	AKR1B1, AKR1C1, AKR1C2, AKR1C3	3.89E-06
GO:0006954	inflammatory response	14	C3, PTGS2, NUPR1, CCL2, IL6, CXCL3, PTX3, IL8, CXCL1, CXCL2, BDKRB1, S100A9, IL1B, IER3	3.89E-06
GO:0044598	doxorubicin metabolic process	4	AKR1B1, AKR1C1, AKR1C2, AKR1C3	3.89E-06
GO:0002237	response to molecule of bacterial origin	10	PTGS2, MMP3, CCL2, IL6, IL8, SOD2, CXCL2, BDKRB1, S100A9, IL1B	7.78E-06
GO:0010033	response to organic substance	25	FGF2, CCL2, CRYAB, SOD2, AKR1C1, RCAN1, ATF3, CXCL2, CHAC1, AKR1C3, PLAT, IL1B, HSPA6, TRIB3, SLC6A12, CSF3, PTGS2, AKR1C2, MMP3, IL6, IGFBP5,	1.27E-05

			IL8, BDKRB1, S100A9, SULF2	
GO:0050900	leukocyte migration	10	NBL1, SLC3A2, CCL2, IL6, CXCL3, IL8, ATP1B1, BDKRB1, IL1B, S100A9	1.54E-05
GO:0008207	C21-steroid hormone metabolic process	5	AKR1B1, AKR1C1, AKR1C2, AKR1C3, FGF2	1.66E-05
GO:0033993	response to lipid	14	PTGS2, MMP3, AKR1C2, CCL2, CRYAB, IL6, IL8, SOD2, RCAN1, BDKRB1, AKR1C3, S100A9, PLAT, IL1B	2.08E-05
GO:0045429	positive regulation of nitric oxide biosynthetic process	5	PTGS2, IL1B, IL6, PTX3, SOD2	2.35E-05
GO:0071395	cellular response to jasmonic acid stimulus	3	AKR1C1, AKR1C2, AKR1C3	2.44E-05
GO:0009753	response to jasmonic acid stimulus	3	AKR1C1, AKR1C2, AKR1C3	2.44E-05
GO:0009617	response to bacterium	11	PTGS2, MMP3, CCL2, IL6, IL8, SOD2, HIST2H2BE, CXCL2, BDKRB1, S100A9, IL1B	2.46E-05
GO:0032496	response to lipopolysaccharide	9	PTGS2, MMP3, CCL2, IL6, IL8, SOD2, BDKRB1, IL1B, S100A9	2.62E-05
GO:0006950	response to stress	31	C3, IL11, SLC3A2, FGF2, CCL2, CRYAB, CXCL3, SOD2, HIST2H2BE, ATF3, CXCL2, ATP1B1, CHAC1, AKR1C3, PLAT, IL1B, HSPA6, IER3, TRIB3, SLC6A12, PTGS2, MMP3, NUPR1, IL6, PTX3, IL8, CXCL1, AKR1B1, BDKRB1, S100A9, CA9	3.19E-05
GO:0042221	response to chemical stimulus	30	NBL1, FGF2, CCL2, CRYAB, CXCL3, SOD2, AKR1C1, RCAN1, ATF3, CXCL2, CHAC1, AKR1C3, PLAT, IL1B, HSPA6, TRIB3, SLC6A12, CSF3, PTGS2, AKR1C2, MMP3, NUPR1, IL6, IGFBP5, IL8, CXCL1, BDKRB1, S100A9, CA9, SULF2	3.19E-05
GO:0032101	regulation of response to external stimulus	11	C3, PTGS2, NBL1, FGF2, CCL2, IL6, IL8, PLAT, IL1B, S100A9, IER3	4.11E-05
GO:0016137	glycoside metabolic process	4	AKR1B1, AKR1C1, AKR1C2, AKR1C3	4.11E-05
GO:0030595	leukocyte chemotaxis	7	NBL1, S100A9, IL1B, CCL2, IL6, CXCL3, IL8	4.11E-05
GO:0010575	positive regulation vascular endothelial growth factor production	4	C3, PTGS2, IL1B, SULF2	6.04E-05
GO:0045428	regulation of nitric oxide biosynthetic process	5	PTGS2, IL1B, IL6, PTX3, SOD2	6.04E-05
GO:0001666	response to hypoxia	9	PTGS2, MMP3, CCL2, CRYAB, SOD2, ATP1B1, PLAT, IL1B, CA9	6.35E-05
GO:0051707	response to other organism	13	PTGS2, MMP3, CCL2, IL6, PTX3, IL8, SOD2, HIST2H2BE, CXCL2, BDKRB1, S100A9, IL1B, IER3	6.35E-05

GO:0036293	response to decreased oxygen levels	9	PTGS2, MMP3, CCL2, CRYAB, SOD2, ATP1B1, PLAT, IL1B, CA9	6.77E-05
GO:0009607	response to biotic stimulus	13	PTGS2, MMP3, CCL2, IL6, PTX3, IL8, SOD2, HIST2H2BE, CXCL2, BDKRB1, S100A9, IL1B, IER3	9.46E-05
GO:0030593	neutrophil chemotaxis	5	S100A9, IL1B, CCL2, CXCL3, IL8	9.46E-05
GO:0002675	positive regulation of acute inflammatory response	4	C3, PTGS2, IL1B, IL6	9.46E-05
GO:0042127	regulation of cell proliferation	18	IL11, FGF2, CCL2, SAT1, SOD2, ATF3, AKR1C3, IL1B, TNFSF9, PTGS2, CSF3, AKR1C2, NUPR1, IL6, IGFBP5, IL8, CXCL1, KLF5	9.46E-05
GO:0070482	response to oxygen levels	9	PTGS2, MMP3, CCL2, CRYAB, SOD2, ATP1B1, PLAT, IL1B, CA9	9.46E-05
GO:0050896	response to stimulus	48	RGS16, IL11, NBL1, CCL2, CRYAB, NYAP1, CXCL3, SOD2, HIST2H2BE, AKR1C1, RCAN1, GDF15, CXCL2, CHAC1, IL1B, PLAT, TNFSF9, IER3, CSF3, AKR1C2, PTX3, AKR1B1, BDKRB1, S100A9, SULF2, C3, SLC3A2, FGF2, WISP1, MYZAP, ATF3, ATP1B1, AKR1C3, RSPO3, HSPA6, GLS, TRIB3, SLC6A12, PTGS2, MMP3, RND3, NUPR1, IL6, IGFBP5, IL8, CXCL1, TNFSF15, CA9	9.97E-05
GO:0060326	cell chemotaxis	7	NBL1, S100A9, IL1B, CCL2, IL6, CXCL3, IL8	1.00E-04
GO:0032103	positive regulation of response to external stimulus	7	C3, PTGS2, S100A9, IL1B, CCL2, IL6, IL8	1.00E-04
GO:0006809	nitric oxide biosynthetic process	5	PTGS2, IL1B, IL6, PTX3, SOD2	1.00E-04
GO:0016477	cell migration	15	PTGS2, NBL1, SLC3A2, MMP3, FGF2, CCL2, IL6, CXCL3, IGFBP5, IL8, ATP1B1, BDKRB1, S100A9, PLAT, IL1B	1.00E-04

(C) GO Molecular Function

Term	Count	Genes	FDR
GO:0005125	cytokine activity	13	CSF3, IL11, FGF2, CCL2, IL6, CXCL3, IL8, CXCL1, GDF15, TNFSF15, CXCL2, IL1B, TNFSF9
GO:0005126	cytokine receptor binding	11	CSF3, IL11, CCL2, IL6, CXCL3, IL8, CXCL1, TNFSF15, CXCL2, IL1B, TNFSF9
GO:0004032	alditol:NADP+ 1-oxidoreductase activity	4	AKR1B1, AKR1C1, AKR1C2, AKR1C3

GO:0047086	ketosteroid monooxygenase activity	3	AKR1C1, AKR1C2, AKR1C3	2.74E-06
GO:0018636	phenanthrene 9,10-monooxygenase activity	3	AKR1C1, AKR1C2, AKR1C3	2.74E-06
GO:0008106	alcohol dehydrogenase (NADP+) activity	4	AKR1B1, AKR1C1, AKR1C2, AKR1C3	4.77E-06
GO:0047115	trans-1,2-dihydrobenzene-1,2-diol dehydrogenase activity	3	AKR1C1, AKR1C2, AKR1C3	6.83E-06
GO:0047023	androsterone dehydrogenase activity	3	AKR1C1, AKR1C2, AKR1C3	6.83E-06
GO:0008083	growth factor activity	8	CXCL1, CSF3, GDF15, IL11, FGF2, IL1B, IL6, INHBE	1.09E-05
GO:0005102	receptor binding	19	C3, IL11, FGF2, CCL2, CXCL3, GDF15, CXCL2, CHAC1, IL1B, TNFSF9, RSPO3, CSF3, ETS2, IL6, IL8, INHBE, CXCL1, TNFSF15, S100A9	1.50E-05
GO:0004033	aldo-keto reductase (NADP) activity	4	AKR1B1, AKR1C1, AKR1C2, AKR1C3	1.57E-05
GO:0008009	chemokine activity	5	CXCL1, CXCL2, CCL2, CXCL3, IL8	2.81E-05
GO:0042379	chemokine receptor binding	5	CXCL1, CXCL2, CCL2, CXCL3, IL8	6.25E-05

(D) GO Cellular Component

Term		Count	Genes	FDR
GO:0005615	extracellular space	22	C3, IL11, FGF2, CCL2, CXCL3, WISP1, GDF15, CXCL2, PLAT, IL1B, TNFSF9, CSF3, MMP3, IL6, IGFBP5, IL8, AKR1B1, CXCL1, TNFSF15, LOXL4, S100A9, SULF2	1.93E-10
GO:0044421	extracellular region part	24	C3, IL11, FGF2, CCL2, CXCL3, WISP1, GDF15, CXCL2, PLAT, IL1B, TNFSF9, PI3, CSF3, MMP3, IL6, IGFBP5, IL8, AKR1B1, CXCL1, TNFSF15, LOXL4, COL5A3, S100A9, SULF2	2.37E-10
GO:0005576	extracellular region	31	C3, IL11, NBL1, FGF2, CCL2, CXCL3, PRSS35, WISP1, SLPI, GDF15, CXCL2, PLAT, IL1B, RSPO3, TNFSF9, PI3, PRRG4, CSF3, MMP3, IL6, IGFBP5, PTX3, IL8, INHBE, AKR1B1, CXCL1, TNFSF15, LOXL4, COL5A3, S100A9, SULF2	9.57E-10