

Supplemental Figures

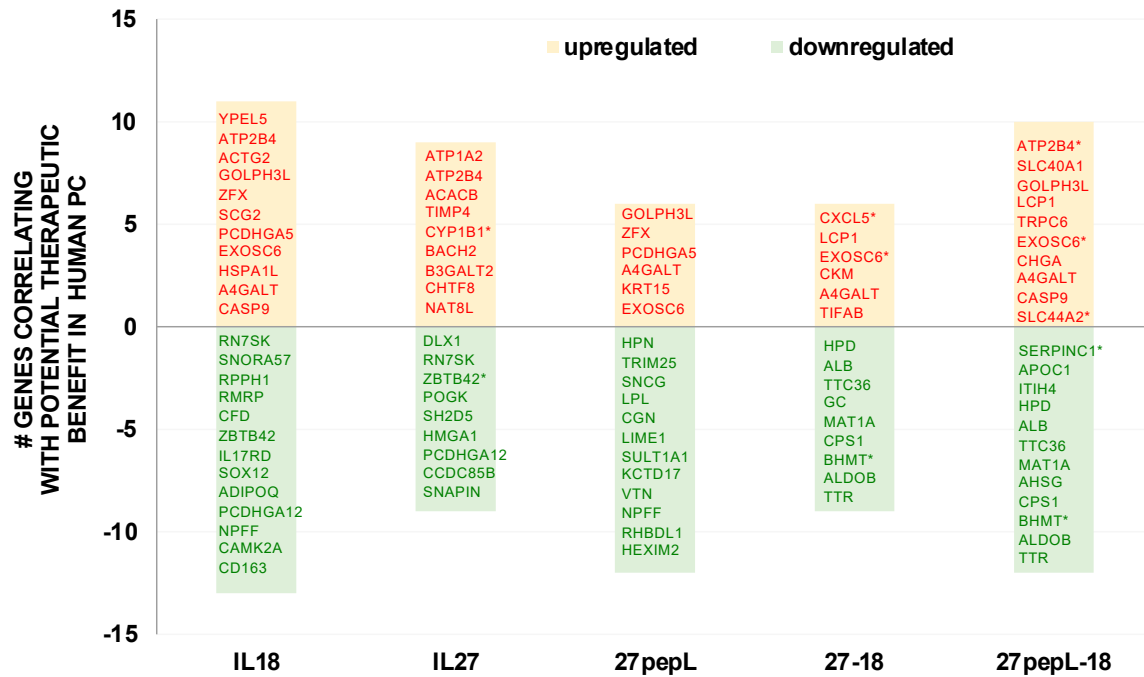


Figure S1. Patterns of Gene Expression and their correlation with potential therapeutic benefit in human prostate tumors. The Cambridge dataset was utilized with camCAPP and ANOVA analysis used to determine Gene Profile and Survival correlations at $p < 0.05$. The top 50 or bottom 50 differentially expressed genes were used from each treatment for this comparison. Red, denotes upregulated genes and Green, denotes downregulated genes. *, gene expression pattern correlates with higher survival (using camCAPP recursive partitioning analysis at $p < 0.05$).

A IL18				B IL27				C 27pepL			
UR: top 30				UR: top 30				UR: top 26			
18 UR	Molecule Type	Activation z-score	B-H corrected p-value	27 Upstream Regulator	Molecule Type	Activation z-score	B-H corrected p-value	27pepL UR	Molecule Type	Activation z-score	B-H corrected p-value
RICTOR	other	4.848	1.03E-09	IFNG	cytokine	8.313	2.13E-73	TNf	cytokine	3.755	5.50E-10
LARP1	translation regulator	4.58	5.99E-13	Interferon alpha	group	6.512	4.77E-37	CSF1	cytokine	2.935	1.38E-03
TNf	cytokine	3.906	7.80E-06	STAT1	transcription regulator	6.454	4.43E-50	CD40	transmembrane receptor	2.716	5.53E-02
PGR	ligand-dependent nuclear receptor	3.513	2.43E-02	IL33	cytokine	6.319	9.45E-36	SIRT3	enzyme	2.629	5.13E-07
TGFb1	growth factor	3.422	2.80E-07	CSF2	cytokine	6.106	1.75E-28	Interferon alpha	group	2.551	7.57E-03
CSF1	cytokine	3.406	1.32E-03	NFkB (complex)	complex	5.901	1.62E-15	Immunoglobulin	complex	2.533	6.94E-06
SIRT3	enzyme	3.301	1.97E-05	IRF7	transcription regulator	5.687	1.28E-22	IL18	cytokine	2.531	6.77E-02
CPT1b	enzyme	3.19	7.84E-06	TGM2	enzyme	5.599	3.93E-14	Tnf (family)	group	2.407	7.20E-02
IL6	cytokine	3.115	2.31E-02	IL5	cytokine	5.552	3.23E-14	IL3	cytokine	2.395	9.81E-03
WNT3A	cytokine	2.965	1.22E-02	SMARCA4	transcription regulator	5.344	9.25E-09	mir-33	microRNA	2.236	2.78E-04
AGT	growth factor	2.946	8.25E-07	AGT	growth factor	5.222	7.20E-26	CCN5	growth factor	2.236	7.99E-03
FLCN	other	2.798	1.04E-04	IRF3	transcription regulator	5.213	4.99E-08	IFNA1/IFNA13	cytokine	2.232	1.05E-02
KLF4	transcription regulator	2.485	3.59E-02	SPI1	transcription regulator	5.184	6.17E-19	miR-2392	mature microRNA	2.235	1.19E-06
SP1	transcription regulator	2.476	2.96E-02	IL2	cytokine	5.144	4.33E-26	FLCN	other	2.232	1.55E-03
KRAS	enzyme	2.454	3.79E-05	IFNA2	cytokine	5.11	1.44E-20	mir-2392	microRNA	2.228	1.19E-06
mir-2392	mature microRNA	2.441	8.25E-07	P38 MAPK	group	5.01	3.83E-09	N-cor	group	2.219	2.72E-04
PDGF BB	complex	2.439	8.25E-07	IL18	cytokine	4.821	7.81E-34	TNFRSF9	transmembrane receptor	2.219	5.77E-04
ERBB2	kinase	2.429	1.12E-04	TLR3	transmembrane receptor	4.777	9.84E-12	CD28	transmembrane receptor	2.137	5.47E-02
ETS1	transcription regulator	2.421	2.55E-02	TNf	cytokine	4.754	2.74E-46	IL15	cytokine	2.117	8.44E-02
NR1H4	ligand-dependent nuclear receptor	2.417	2.55E-02	NONO	transcription regulator	4.748	2.86E-12	CSF2	cytokine	2.079	7.02E-02
NFAT5	transcription regulator	2.393	4.94E-02	Igf	complex	4.71	6.51E-20	RELA	transcription regulator	2.052	3.97E-02
PI3K (complex)	complex	2.386	2.20E-02	ELAVL1	other	4.629	2.89E-11	MEX3A	other	2	1.39E-02
TEAD4	transcription regulator	2.373	1.43E-03	TLR9	transmembrane receptor	4.585	9.84E-12	MALAT1	other	2	1.76E-02
IL3	cytokine	2.297	4.27E-03	G protein alpai	group	4.583	3.86E-20	ASXL1	transcription regulator	2	1.87E-02
RET	kinase	2.217	8.84E-03	ARNT2	transcription regulator	4.583	4.81E-07	USP22	peptidase	2	1.98E-02
Ccl2	cytokine	2.177	4.34E-02	SIM1	transcription regulator	4.571	3.07E-12	Msp3k7	kinase	2	5.88E-02
CTNNB1	transcription regulator	2.174	9.54E-16	MYD88	transmembrane receptor	4.567	2.02E-12				
PTH	other	2.158	3.93E-03	TLR4	transmembrane receptor	4.499	2.17E-19				
P38 MAPK	group	2.128	2.49E-03	---	---	---	---				
UR: bot 18				UR: bot 30				UR: bot 30			
PPARGC1B	transcription regulator	-2.02	1.07E-02	COP1	enzyme	-2.97	3.82E-07	MLXIPL	transcription regulator	-2.415	3.02E-03
MALSU1	other	-2.236	6.24E-06	mir-155	microRNA	-2.987	4.66E-04	BCL6	transcription regulator	-2.415	6.96E-02
MRPL14	other	-2.236	1.84E-05	RNF31	enzyme	-3	4.85E-04	MRPL12	other	-2.423	1.43E-08
PTCD1	other	-2.236	1.48E-04	NRAS	enzyme	-3.048	1.38E-13	HNFAcEs dimer	complex	-2.425	1.33E-06
LONP1	peptidase	-2.309	8.06E-07	GFI1	transcription regulator	-3.064	1.51E-04	T3-TR-RXR	complex	-2.425	4.01E-04
ALKBH1	enzyme	-2.449	8.25E-07	miR-34a-5p (and other miRNA	mature microRNA	-3.148	6.46E-03	PPARGC1B	transcription regulator	-2.438	5.49E-03
NSUN3	enzyme	-2.449	8.25E-07	CBS	transcription regulator	-3.162	2.75E-03	GC-GCR dimer	complex	-2.449	5.25E-06
CAB39L	kinase	-2.478	2.52E-05	miR-155-5p (miRNAs w/seed	mature microRNA	-3.238	8.95E-03	Uf	cytokine	-2.559	6.36E-07
FASN	enzyme	-2.607	2.56E-02	PTGER4	G-protein coupled receptor	-3.256	4.51E-15	CREBBP	transcription regulator	-2.577	2.24E-03
MRPL12	other	-2.613	1.16E-08	NCSTN	peptidase	-3.302	1.08E-08	SOCs1	other	-2.607	2.36E-02
ADAM12	peptidase	-2.8	1.27E-02	RC3H1	enzyme	-3.302	2.96E-08	CEBPA	transcription regulator	-2.615	2.05E-12
TWNK	enzyme	-2.813	5.56E-06	IL1RN	cytokine	-3.324	7.89E-09	ESR2	ligand-dep. nuclear receptor	-2.643	7.74E-03
Lh	complex	-3.139	3.77E-08	APOE	transporter	-3.618	4.36E-16	KDM6A	enzyme	-2.646	3.33E-05
DAF3	other	-3.162	1.36E-11	MAPK1	kinase	-3.656	1.29E-10	PKD1	ion channel	-2.714	2.11E-03
DDX5	enzyme	-3.512	9.50E-09	ZC3H12C	other	-3.675	2.65E-13	NFE2L2	transcription regulator	-2.791	9.48E-09
MYCN	transcription regulator	-3.52	2.75E-08	SMARCA5	transcription regulator	-3.691	3.00E-13	ACOX1	enzyme	-2.794	2.61E-14
MYC	transcription regulator	-4.096	8.46E-13	PSMB11	peptidase	-3.71	5.10E-11	PPARGC1A	transcription regulator	-2.811	1.06E-05
MLXIPL	transcription regulator	-5.251	4.32E-18	TGFB2	kinase	-3.825	6.24E-08	Hmg3n	other	-2.813	6.93E-16
				PIK3CG	kinase	-4.055	2.36E-24	TWNK	enzyme	-2.813	3.82E-08
				ACKR2	G-protein coupled receptor	-4.085	3.32E-15	DAP3	other	-2.828	1.95E-10
				PNPT1	enzyme	-4.333	1.32E-16	LONP1	peptidase	-2.828	2.52E-04
				IL10RA	transmembrane receptor	-4.397	6.25E-47	FST	other	-2.985	1.22E-05
				SIRT1	transcription regulator	-4.401	1.40E-21	PEBP1	other	-3	3.08E-07
				ETV6-RUNX1	fusion gene/product	-4.428	1.05E-11	FASN	enzyme	-3.36	4.62E-12
				HOXA10	transcription regulator	-4.447	1.25E-08	NR3C1	ligand-dep. nuclear receptor	-3.428	1.51E-09
				TRIM24	transcription regulator	-4.572	1.27E-15	PPARG	ligand-dep. nuclear receptor	-3.498	5.96E-14
				INSIG1	other	-4.929	1.26E-16	ADIPOQ	other	-3.797	7.23E-23
				SOCs1	other	-4.949	2.34E-21	SMARCB1	transcription regulator	-4.078	4.41E-08
				Irgm1	other	-4.995	2.06E-18	HNFA4A	transcription regulator	-4.225	4.23E-07
				mir-21	microRNA	-5.972	2.87E-19	HNFA1A	transcription regulator	-4.457	2.73E-18

Figure S2. Upstream Regulators (UR) from IPA analyses, single therapies. (A) UR predicted in IL-18-treated tumors; (B) UR in IL27-treated tumors; (C) UR in IL-27pepL-treated tumors. *Red*, predicted as activated upstream regulators and ranked by z-score; *Green*, predicted as inhibited upstream regulators, ranked by z-score. Shown are the UR meeting the cutoff of activation z-score >2.0 or <-2.0 and a B-H corrected p value < 0.05.

A 27→18

UR: top 30

27_18 UR	Molecule Type	Activation z-score	B-H corrected p-value
IFNG	cytokine	3.681	1.04E-08
CSF1	cytokine	3.655	2.31E-06
IL21	cytokine	3.383	5.64E-04
TLR4	transmembrane receptor	3.204	1.40E-04
LDL	complex	3.177	5.42E-03
MYD88	other	3.06	8.44E-05
P38 MAPK	group	3.05	1.00E-02
TLR3	transmembrane receptor	2.92	4.62E-02
CSF2	cytokine	2.886	8.97E-03
IL2	cytokine	2.873	3.60E-02
IL5	cytokine	2.872	1.84E-02
PARP1	enzyme	2.809	7.00E-03
IL1B	cytokine	2.803	2.36E-07
FFAR3	G-protein coupled receptor	2.739	3.68E-06
TGM2	enzyme	2.714	1.02E-02
TNF	cytokine	2.681	1.50E-05
F2RL1	G-protein coupled receptor	2.621	1.37E-03
CARD9	other	2.611	1.86E-05
STAT1	transcription regulator	2.61	4.56E-11
APP	other	2.513	1.19E-06
IL17A	cytokine	2.482	1.20E-02
TNFSF11	cytokine	2.465	4.85E-03
USP22	peptidase	2.449	1.08E-03
SELP1G	other	2.449	1.08E-03
HRG	other	2.449	2.02E-05
LGALS3	other	2.425	5.16E-03
PF4	cytokine	2.416	1.19E-02
Ige	complex	2.412	1.54E-03
HMGB1	transcription regulator	2.41	5.40E-03
IL3	cytokine	2.4	1.96E-03

UR: bot 30

USF2	transcription regulator	-2.2	8.78E-03
AIRE	transcription regulator	-2.2	4.30E-03
RNF31	enzyme	-2.2	2.63E-03
Td 1/3/4	group	-2.2	4.15E-07
ST8SIA1	enzyme	-2.207	3.79E-04
B4GALNT1	enzyme	-2.207	4.17E-05
TRIM24	transcription regulator	-2.236	4.61E-02
HHB	transporter	-2.236	7.79E-03
LIPE	enzyme	-2.236	2.67E-05
PPARG	ligand-dependent nuclear receptor	-2.306	6.11E-08
PKD1	ion channel	-2.331	1.73E-03
SCD	enzyme	-2.387	1.96E-03
PXR ligand-PXR-Retinoic acid complex	complex	-2.395	1.08E-03
BCL6	transcription regulator	-2.399	2.98E-02
miR-21	microRNA	-2.413	9.97E-05
HNF4A dimer	complex	-2.425	3.70E-06
FST	other	-2.449	7.47E-03
SMTNL1	other	-2.449	1.50E-04
NR3C1	ligand-dependent nuclear receptor	-2.485	6.13E-05
ZC3H12C	other	-2.611	2.25E-05
KDM6A	enzyme	-2.646	8.99E-05
Hmgn3	other	-2.813	1.90E-13
CFTR	ion channel	-2.905	1.11E-06
PTGER4	G-protein coupled receptor	-2.97	2.87E-03
SOCS1	other	-2.985	1.48E-03
ACOX1	enzyme	-3.186	3.72E-13
IL10RA	transmembrane receptor	-3.595	6.65E-13
HNF4A	transcription regulator	-3.841	2.13E-09
ADIPOQ	other	-4.069	6.57E-20
HNF1A	transcription regulator	-4.345	2.81E-16

B 27pepL→18

UR: top 30

27pL 18 UR	Molecule Type	Activation z-score	B-H corrected p-value
CSF1	cytokine	3.773	9.94E-09
TNF	cytokine	3.481	1.23E-15
RELA	transcription regulator	3.326	1.63E-03
CSF2	cytokine	3.266	2.35E-03
Ige	complex	3.162	2.71E-05
TNFSF12	cytokine	3.062	1.12E-04
IL1B	cytokine	2.936	1.13E-09
TLR3	transmembrane receptor	2.889	2.27E-03
ERK1/2	group	2.883	1.12E-04
APP	other	2.866	1.93E-05
SPP1	cytokine	2.8	1.82E-03
MAPKAPK2	kinase	2.789	5.91E-05
IL33	cytokine	2.788	5.54E-06
KITLG	growth factor	2.778	6.71E-04
NFKB1	transcription regulator	2.723	3.44E-07
LDL	complex	2.672	1.15E-03
TNFSF11	cytokine	2.647	1.70E-06
IL1A	cytokine	2.647	2.54E-06
SIRT3	enzyme	2.629	1.02E-06
EGR1	transcription regulator	2.626	4.13E-05
CCK1	other	2.618	3.12E-03
cytokine	group	2.611	1.54E-02
SLC27A2	transporter	2.606	7.60E-05
IL18	cytokine	2.592	1.94E-03
Ccl2	cytokine	2.579	6.71E-05
IL21	cytokine	2.555	3.55E-03
MYD88	other	2.545	1.42E-04
MAP2K1	kinase	2.543	4.84E-05
HRG	other	2.449	1.15E-05
collagenase	group	2.449	1.44E-04

UR: bot 30

ALKBH1	enzyme	-2.236	1.71E-06
NSUN3	enzyme	-2.236	1.71E-06
PSEN1	peptidase	-2.277	8.86E-03
PXR ligand-R complex	complex	-2.395	6.54E-04
MLXIP1	transcription regulator	-2.415	1.21E-03
HNF4A dimer	complex	-2.425	2.11E-06
COP1	enzyme	-2.425	1.03E-04
PPARGC1B	transcription regulator	-2.438	6.08E-03
LONP1	peptidase	-2.449	1.89E-03
NR3C1	ligand-dependent nuclear receptor	-2.531	4.72E-07
LIF	cytokine	-2.559	4.08E-07
MED1	transcription regulator	-2.563	1.20E-04
VIP	other	-2.617	9.43E-03
GFI1	transcription regulator	-2.63	4.58E-03
DAP3	other	-2.646	2.04E-08
KDM6A	enzyme	-2.646	4.98E-05
ADIPOQ	other	-2.721	1.45E-26
CFTR	ion channel	-2.744	5.92E-07
ADAM12	peptidase	-2.779	8.42E-07
Hmgn3	other	-2.813	6.32E-14
LIPE	enzyme	-2.813	7.47E-05
PPARGC1A	transcription regulator	-2.96	7.72E-07
BCL6	transcription regulator	-2.97	4.45E-02
FST	other	-2.985	2.06E-05
FASN	enzyme	-3.06	3.19E-09
SOCS1	other	-3.081	1.96E-04
SMARCB1	transcription regulator	-3.395	2.35E-08
PPARG	ligand-dependent nuclear receptor	-3.483	3.05E-14
HNF4A	transcription regulator	-3.819	5.12E-10
HNF1A	transcription regulator	-4.457	1.32E-18

Figure S3. Upstream Regulators from IPA analyses for the combination therapies. Red, predicted as activated upstream regulators and ranked by z-score; Green, predicted as inhibited upstream regulators, ranked by z-score. Shown is also the p-value of the overlap.

Supplementary Table

Table S1. Gene expression signatures utilized in the EPIC RNAseq cell profiling analyses.

Signature name	Bulk Expression File	FKPM, Counts	Source	Reference Expression File	Source
LMPP_gsea	GSE116177	FKPM	Haemopedia	GSE15330, M7021	GSEA, immusigdb
GMP_gsea	GSE116177	FKPM	Haemopedia	GSE15330, M7041	GSEA, immusigdb
MPP_gsea	GSE116177	FKPM	Haemopedia	GSE22432, M7817	GSEA, immusigdb
gMDSC_gsea	GSE140029	FKPM	Ref. ⁴²	GSE24102, M4541	GSEA, immusigdb
mMDSC_gsea	GSE140029	FKPM	Ref. ⁴²	GSE23502, M8087	GSEA, immusigdb
MDSC_gsea	GSE140029	FKPM	Ref. ⁴²	GSE21927, M7563	GSEA, immusigdb
HSC1_gsea	GSE109125	Cts	ImmGen ULI	GSE15330, M7060	GSEA, immusigdb
HSC2_gsea	GSE109125	Cts	ImmGen ULI	GSE15330, M7018	GSEA, immusigdb
Macro_gsea	GSE109125	Cts	Immgen	GSE27859, M8590	GSEA, immusigdb
NKT_gsea2	GSE109125	Cts	Immgen	GSE27786, M4870	GSEA, immusigdb
CD8_Teff_gsea	GSE109125	Cts	Immgen	GSE1000002, M3027	GSEA, immusigdb
Bcell_gsea	GSE109125	Cts	Immgen	GSE27786, M4799	GSEA, immusigdb
Neutr_gsea	GSE109125	Cts	Immgen	GSE27786, M4880	GSEA, immusigdb
Treg_gsea	GSE109125	Cts	Immgen	GSE13306, M3229	GSEA, immusigdb
CD8_T_gsea	GSE109125	Cts	Immgen	GSE1000002, M3035	GSEA, immusigdb
cDC_gsea	GSE109125	Cts	Immgen	GSE3691, M6363	GSEA, immusigdb
DC8a_gsea	GSE109125	Cts	Immgen	GSE12392, M7135	GSEA, immusigdb
pDC1_gsea	GSE109125	Cts	Immgen	GSE22432, M7835	GSEA, immusigdb
pDC2_gsea	GSE109125	Cts	Immgen	GSE3691, M6368	GSEA, immusigdb
NK11_gsea	GSE109125	Cts	Immgen	GSE13229, M3213	GSEA, immusigdb
NK27_gsea	GSE109125	Cts	Immgen	GSE13229, M3205	GSEA, immusigdb
NK27_11_gsea	GSE109125	Cts	Immgen	GSE13229, M3209	GSEA, immusigdb
M2_gsea	GSE109125	Cts	Immgen	GSE18804, GEO2R analysis	GSEA, immusigdb
Tgd_gsea	GSE109125	Cts	Immgen	GSE22196, M7655	GSEA, immusigdb
Th2_gsea	GSE109125	Cts	Immgen	GSE14026, M3164	GSEA, immusigdb
Th1_gsea	GSE109125	Cts	Immgen	GSE14026, M3356	GSEA, immusigdb
NKT_gsea	GSE109125	Cts	Immgen	GSE3039, M6429	GSEA, immusigdb
M1_gsea	GSE109125	Cts	Immgen	GSE26912, M8205	GSEA, immusigdb
Plasma_gsea	GSE109125	Cts	Immgen	GSE4142, M6395	GSEA, immusigdb

Shown are signature names, bulk and reference files used and sources.