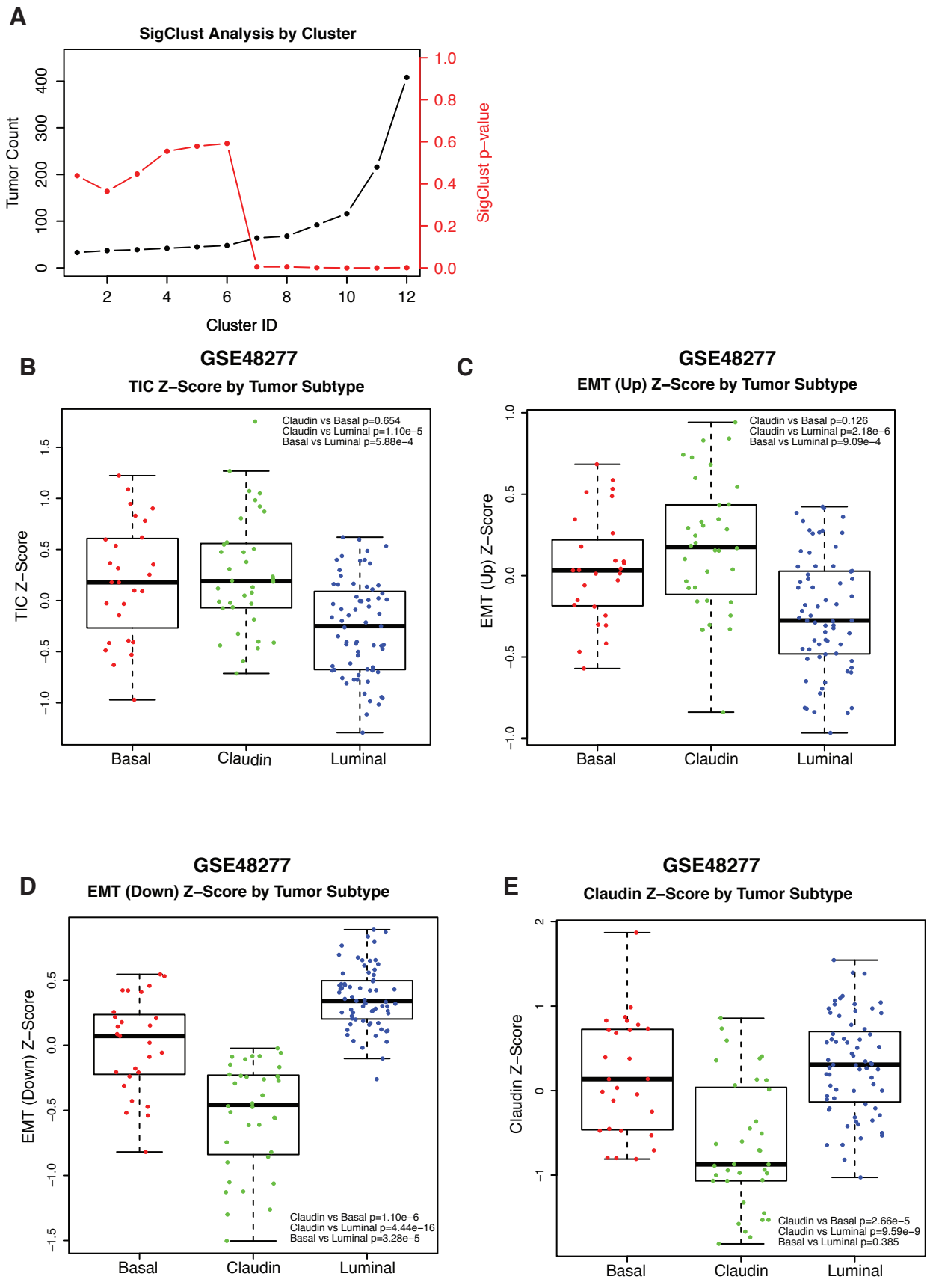
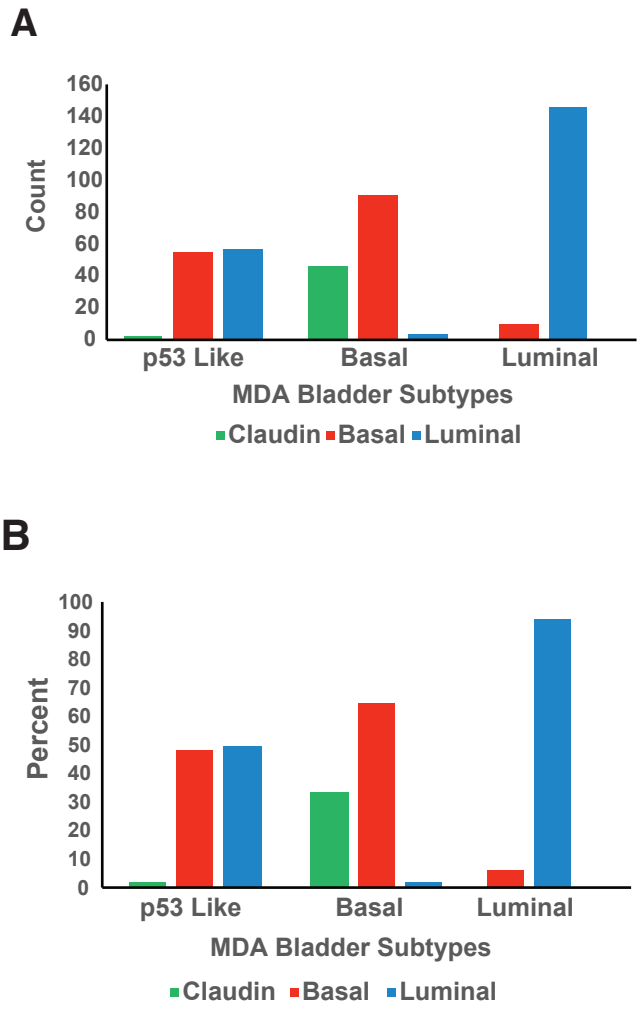
Supplementary Figure 1



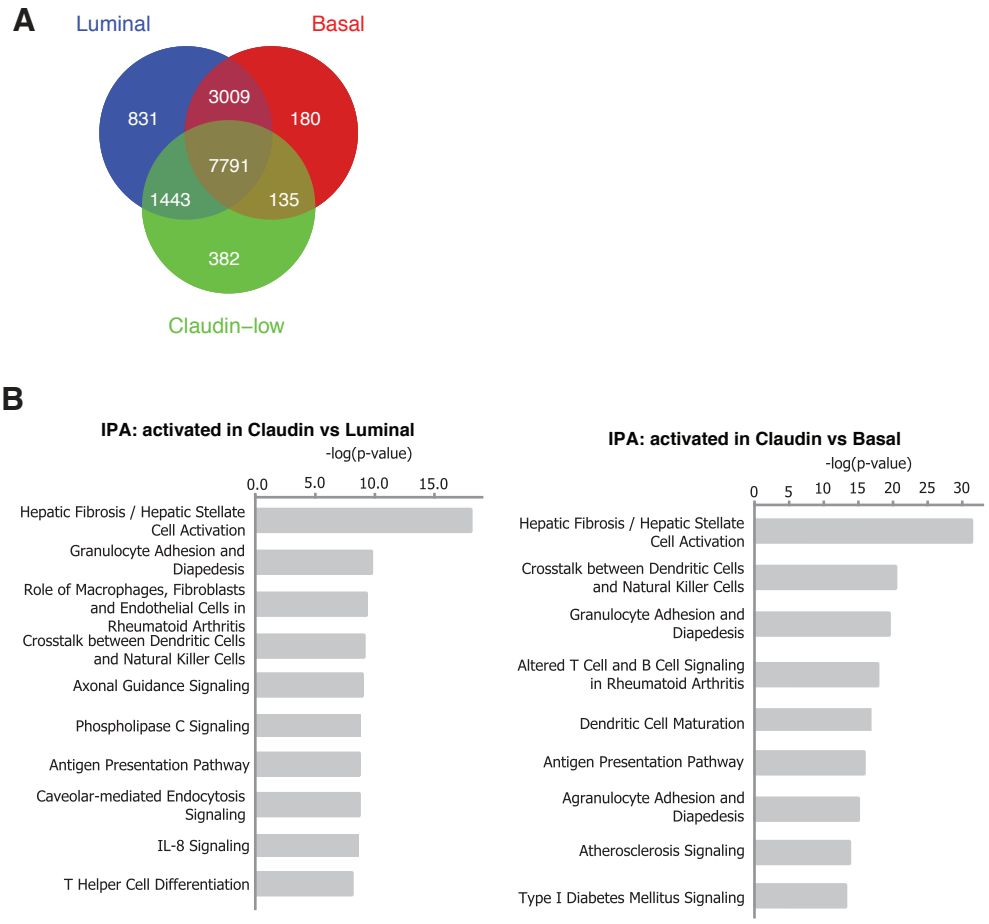
Supplementary Figure 1.
(A) Plot indicating the number of tumors and the associated SigClust p-value across all clusters tested through SigClust Gaussian distribution analysis. Significance was calculate using SigClust software. n=408. **(B-E)** Boxplots showing the Z-Scores of the TIC, EMT (Up and Down) and Claudin gene signatures by predicted subtype across the validation metadataset. Significance was calculated using a t-test with a Bonferroni correction. n=130.

Supplementary Figure 2



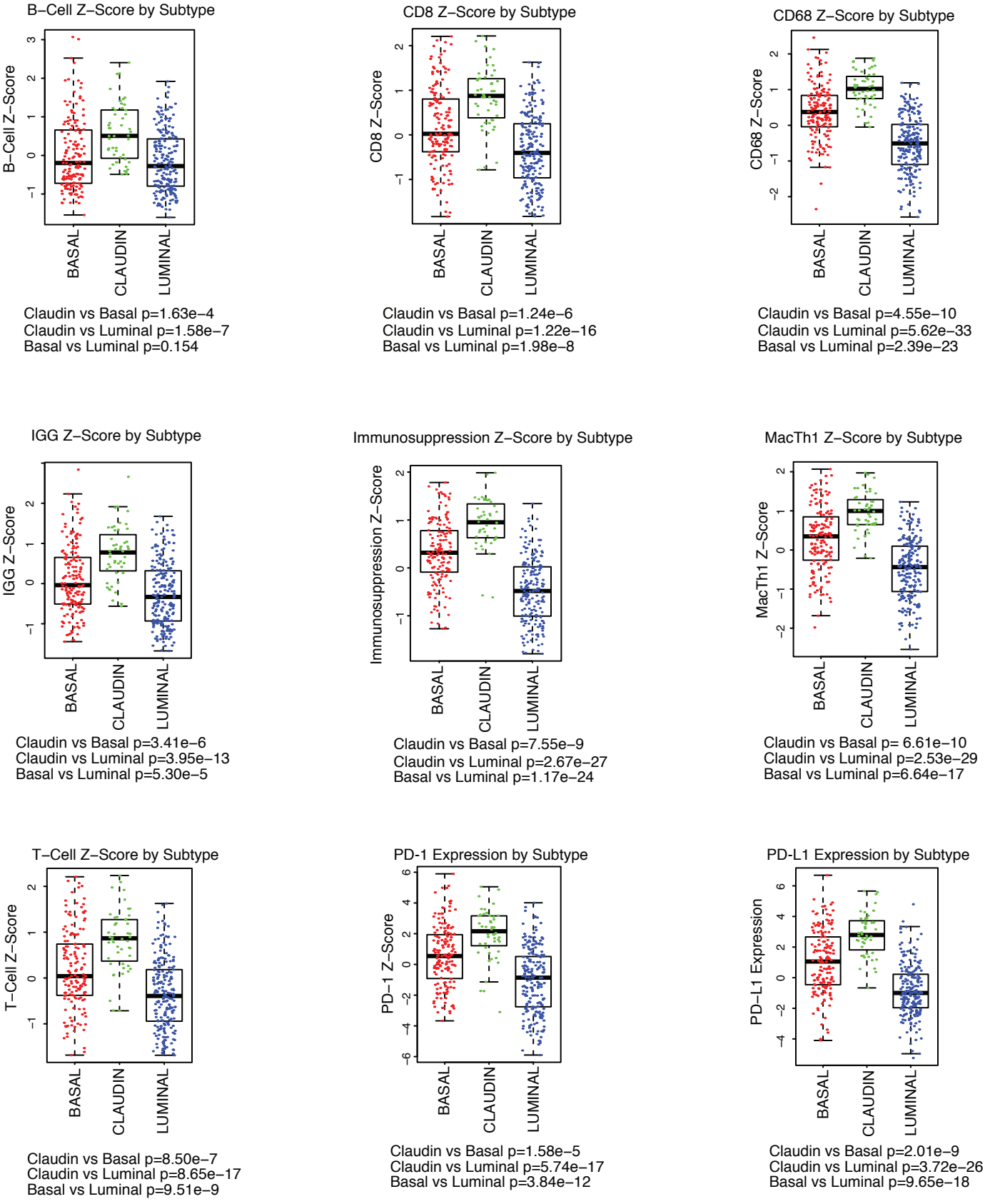
Supplementary Figure 2.
(A-B) Barplots showing the classification of TCGA urothelial carcinoma tumors by the M.D. Anderson McConkey group (x-axis) and our subtype classifications (y-axis) by count and percent. n=408.

Supplementary Figure 3



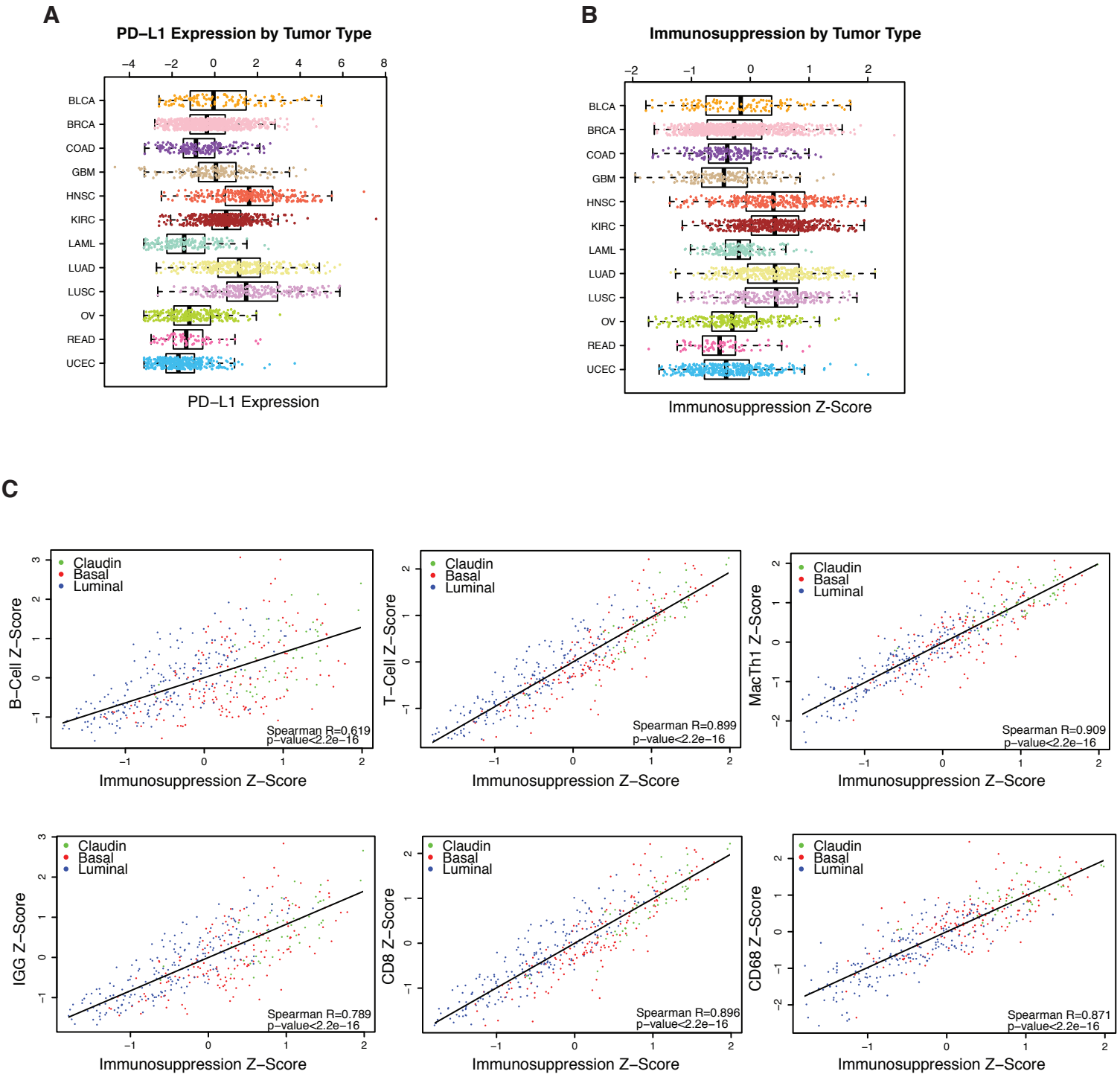
Supplementary Figure 3.
(A) Venn diagram of gene counts that are significantly uniquely differentially expressed (FDR=0.05) in the TCGA claudin-low, basal, and luminal subtypes. Significance was calculated using Significant Analysis of Microarrays (SAM) software. n=408. **(B)** Barplot of the most significantly activated signaling pathways in Claudin-low tumors compared to both Basal and Luminal tumors. Significance was determined using Ingenuity Pathway Analysis (IPA) software. n=408.

Supplementary Figure 4



Supplementary Figure 4.
Boxplots showing the Z-Scores of the B-Cell, CD8+ T-Cell, CD68+ tumor associated Macrophage, Immunoglobulin, Immune Suppression, Macrophage, and T-cell and the RNA expression of PD-1 and PD-L1 across Claudin-low, Basal, and Luminal subtypes in the TCGA dataset. Significance was calculated using a t-test with a Bonferroni correction. n=408.

Supplementary Figure 5



Supplementary Figure 5.
(A-B) Boxplots of PD-L1 expression and Immunosuppression Z-Score across the PanCancer bladder urothelial carcinoma (BLCA), breast cancer (BRCA), colon adenocarcinoma (COAD), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), acute myeloid leukemia (LAML), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), ovarian serous cystadenocarcinoma (OV), rectum adenocarcinoma (READ), and uterine corpus endometrial carcinoma (UCEC). n=3602 **(C)** Correlation plots of the Immunosuppression gene signature with the B-Cell, T-Cell, Macrophage, Immunoglobulin, CD8+ T-cell, and CD68+ tumor associated Macrophage gene signatures with an associated best fit line. Correlation coefficient and significance was calculated using a Spearman's rank test.

SupplementaryTable 1: Bladder EMT Signature Genelist

Gene Symbol	Entrezgene ID	EMT Regulation
ZFHX4	79776	Upregulated
XIST	7503	Upregulated
VIM	7431	Upregulated
UCHL1	7345	Upregulated
TUBB2B	347733	Upregulated
TMSB15A	11013	Upregulated
TCF4	6925	Upregulated
STOM	2040	Upregulated
SLIT2	9353	Upregulated
SELM	140606	Upregulated
RADIL	55698	Upregulated
POLE4	56655	Upregulated
PNMAL1	55228	Upregulated
PLOD2	5352	Upregulated
PDGFC	56034	Upregulated
PABPC4L	132430	Upregulated
MSRB3	253827	Upregulated
MSN	4478	Upregulated
MOXD1	26002	Upregulated
MCAM	4162	Upregulated
MAPRE2	10982	Upregulated
MAGED4B	81557	Upregulated
LDOC1	23641	Upregulated
KLF12	11278	Upregulated
KCTD12	115207	Upregulated
IGF2BP1	10642	Upregulated
HOXC4	3221	Upregulated
HOXB9	3219	Upregulated
HES5	388585	Upregulated
GSTP1	2950	Upregulated
GALNTL1	57452	Upregulated
FKBP10	60681	Upregulated
FBN2	2201	Upregulated
FAM69B	138311	Upregulated
FAM155B	27112	Upregulated
EEF1A2	1917	Upregulated
DNAJC6	9829	Upregulated

DIRAS1	148252	Upregulated
DCP1B	196513	Upregulated
DACH1	1602	Upregulated
CPS1	1373	Upregulated
CPE	1363	Upregulated
COLEC12	81035	Upregulated
CMTM3	123920	Upregulated
CKB	1152	Upregulated
CDK6	1021	Upregulated
CAND2	23066	Upregulated
C10orf125	282969	Upregulated
BEX4	56271	Upregulated
ALDH2	217	Upregulated
VGLL1	51442	Downregulated
UGT1A6	54578	Downregulated
UCA1	652995	Downregulated
TRIM29	23650	Downregulated
TNS4	84951	Downregulated
TNFAIP2	7127	Downregulated
TMEM45B	120224	Downregulated
TMEM30B	161291	Downregulated
TM4SF1	4071	Downregulated
THBD	7056	Downregulated
TACSTD2	4070	Downregulated
SPINT1	6692	Downregulated
SLC16A5	9121	Downregulated
S100P	6286	Downregulated
S100A6	6277	Downregulated
RPS4Y1	6192	Downregulated
PPP1R3C	5507	Downregulated
PLBD1	79887	Downregulated
OVOL1	5017	Downregulated
OCIAD2	132299	Downregulated
NIPAL4	348938	Downregulated
MLH1	4292	Downregulated
MGMT	4255	Downregulated
LXN	56925	Downregulated
LAD1	3898	Downregulated
KRT19	3880	Downregulated

HSD17B2	3294	Downregulated
HS3ST1	9957	Downregulated
HPGD	3248	Downregulated
FABP4	2167	Downregulated
ERP27	121506	Downregulated
EPCAM	4072	Downregulated
ELF3	1999	Downregulated
EHF	26298	Downregulated
EFS	10278	Downregulated
DENND2D	79961	Downregulated
CST1	1469	Downregulated
CLDN1	9076	Downregulated
CDH1	999	Downregulated
C19orf33	64073	Downregulated
C10orf99	387695	Downregulated
C10orf116	10974	Downregulated
BTBD16	118663	Downregulated
BATF	10538	Downregulated
ARHGDIB	397	Downregulated
ANXA8L2	728113	Downregulated
ALDH1L1	10840	Downregulated
AKR1C3	8644	Downregulated
AGR2	10551	Downregulated
ABCC3	8714	Downregulated

Supplementary Table 2: Claudin Breast and Bladder Classifications

		Breast Classifier	
		Claudin	Other
Bladder Classifier	Claudin	36	12
	Other	47	313

p=1.10e-18

Supplementary Table 3: BCL40 Genelist

Gene Name	EntrezGene ID
GPX2	2877
UPK1A	11045
KLHDC7A	127707
SNX31	169166
BMP3	651
PDCD1LG2	80380
CACNA1D	776
BCAS1	8537
LRRC15	131578
SPINK1	6690
TOX3	27324
HMGCS2	3158
SLC9A2	6549
FMO1	2326
L1CAM	3897
COL11A1	1301
KRT6B	3854
FAM3B	54097
KANK4	163782
MT2A	4502
KRT81	3887
F3	2152
SLC14A1	6563
FAM190A	401145
SIGLEC10	89790
SPHK1	8877
CYP4F12	66002
SCNN1G	6340
DHRS2	10202
PPAPDC1A	196051
GPR84	53831
FAM101A	144347
ALDH1L1	10840
VSIG2	23584
SAA1	6288
SERPINA1	5265
FAM176A	84141

SCNN1B	6338
TNFAIP6	7130
GRHL3	57822

Supplementary Table 6: Ingenuity Pathway Analysis Upstream Regulators Summary

Claudin-low vs Basal

Upstream Regulator	Molecule Type	Predicted Activation State	Activation Z-Score	p-value of overlap
IFNG	cytokine	Activated	11.209	3.44E-79
TNF	cytokine	Activated	11.204	8.64E-70
TGFB1	growth factor	Activated	6.016	3.61E-55
IL4	cytokine	Activated	3.652	2.34E-41
TCR	complex	Activated	5.077	1.86E-39
NFkB (complex)	complex	Activated	7.016	2.48E-39
Alpha catenin	group	Inhibited	-6.91	2.06E-36
MAPK1	kinase	Inhibited	-5.06	1.28E-34
IL13	cytokine		1.219	1.44E-34
IL1B	cytokine	Activated	6.028	5.94E-34
TP53	transcription regulator		1.278	1.49E-33
SMARCA4	transcription regulator	Activated	7.76	6.37E-33
TGM2	enzyme	Activated	8.182	1.34E-32
STAT1	transcription regulator	Activated	6.177	8.33E-32
TLR4	transmembrane receptor	Activated	6.512	2.94E-29
IFNL1	cytokine	Activated	6.388	7.41E-29
P38 MAPK	group	Activated	5.623	1.10E-27
RELA	transcription regulator	Activated	5.166	4.19E-27
IL27	cytokine	Activated	4.187	4.20E-27
TREM1	transmembrane receptor	Activated	3.366	9.48E-27
STAT3	transcription regulator	Activated	4.613	1.67E-26
CD3	complex	Inhibited	-4.482	1.70E-26
IL12 (complex)	complex	Activated	4.857	2.52E-26
MYD88	other	Activated	5.86	6.40E-26
Ifnar	group	Activated	6.653	7.15E-26

TLR3	transmembrane receptor	Activated	6.413	3.19E-25
IL1A	cytokine	Activated	6.03	1.26E-24
FAS	transmembrane receptor	Inhibited	-2.94	1.79E-24
IL1RN	cytokine	Inhibited	-6.905	3.37E-24
TLR7	transmembrane receptor	Activated	6.035	5.10E-24
TLR9	transmembrane receptor	Activated	7.042	8.06E-24
IFNA2	cytokine	Activated	7.125	9.92E-24
PRL	cytokine	Activated	6.718	2.23E-23
AHR	ligand-dependent nuclear receptor	Inhibited	-3.688	8.27E-22
estrogen receptor	group	Inhibited	-5.151	1.09E-21
SPI1	transcription regulator		1.967	1.33E-21
APOE	transporter	Inhibited	-3.286	3.17E-21
PTGER4	g-protein coupled receptor	Inhibited	-4.462	5.20E-21
IRF1	transcription regulator	Activated	3.986	1.55E-20
IL17A	cytokine	Activated	3.73	4.34E-20
IL10RA	transmembrane receptor	Inhibited	-3.858	9.61E-20
CD44	enzyme	Activated	4.026	9.87E-20
mir-21	microrna	Inhibited	-4.578	6.27E-19
Cg	complex	Activated	3.799	6.53E-19
ERK1/2	group	Activated	2.895	8.81E-19
IL10	cytokine		0.085	1.17E-18
IFNB1	cytokine	Activated	5.044	1.23E-18

Claudin-low vs Luminal

Upstream Regulator	Molecule Type	Predicted Activation State	Activation Z-Score	p-value of overlap
TNF	cytokine	Activated	11.157	7.43E-59
TGFB1	growth factor	Activated	6.801	2.78E-53
IFNG	cytokine	Activated	10.869	7.34E-53
TP53	transcription regulator		0.683	3.34E-38
IL4	cytokine	Activated	3.438	4.86E-32
Alpha catenin	group	Inhibited	-8.435	3.16E-31
NFkB (complex)	complex	Activated	8.372	8.51E-31
TCR	complex	Activated	5.377	5.67E-30
ERBB2	kinase	Activated	6.358	8.19E-30
IL13	cytokine		1.382	2.13E-29
SMARCA4	transcription regulator	Activated	7.418	3.69E-29
MAPK1	kinase	Inhibited	-4.438	4.76E-29
TGM2	enzyme	Activated	7.329	8.16E-27
estrogen receptor	group	Inhibited	-6.22	1.86E-25
TREM1	transmembrane receptor	Activated	4.289	2.45E-25
IL1B	cytokine	Activated	7.39	2.52E-25
STAT3	transcription regulator	Activated	5.814	1.20E-23
IFNL1	cytokine	Activated	6.828	1.78E-22
IL27	cytokine	Activated	4.108	2.72E-22
STAT1	transcription regulator	Activated	5.659	5.64E-21
STAT5A	transcription regulator		1.328	7.19E-21
CD3	complex	Inhibited	-5.175	5.15E-20
Ifnar	group	Activated	6.863	7.28E-20
FAS	transmembrane receptor	Inhibited	-2.198	7.58E-20
Cg	complex	Activated	5.246	2.13E-19
CREBBP	transcription regulator		-0.418	4.51E-19
P38 MAPK	group	Activated	5.871	6.41E-19
IL12 (complex)	complex	Activated	4.355	7.50E-19

TLR4	transmembrane receptor	Activated	7.544	9.99E-19
PRL	cytokine	Activated	6.005	1.40E-17
RELA	transcription regulator	Activated	5.853	2.34E-17
IFNA2	cytokine	Activated	6.878	4.28E-17
IL10RA	transmembrane receptor	Inhibited	-3.866	6.13E-17
ID3	transcription regulator		0.058	9.63E-17
ID2	transcription regulator		-0.783	1.65E-16
AHR	ligand-dependent nuclear receptor	Inhibited	-2.61	8.20E-16
IL2	cytokine	Activated	4.967	8.62E-16
APOE	transporter	Inhibited	-4.445	8.67E-16
IL1A	cytokine	Activated	7.013	8.71E-16
EP300	transcription regulator		0.973	9.37E-16
SATB1	transcription regulator		-0.443	1.02E-15
ERK1/2	group	Activated	3.079	1.05E-15
CTNNB1	transcription regulator	Activated	4.479	1.20E-15
NR3C1	ligand-dependent nuclear receptor		-1.879	1.28E-15
FSH	complex		0.792	1.40E-15
ESR1	ligand-dependent nuclear receptor		0.548	2.51E-15
IFNB1	cytokine	Activated	4.642	2.58E-15

Basal vs Luminal

Upstream Regulator	Molecule Type	Predicted Activation State	Activation Z-Score	p-value of overlap
TNF	cytokine	Activated	9.73	1.13E-40
TGFB1	growth factor	Activated	5.786	1.84E-40
TP53	transcription regulator		-0.395	3.02E-37
IFNG	cytokine	Activated	9.036	2.76E-31
ERBB2	kinase	Activated	5.96	7.79E-29
SMARCA4	transcription regulator	Activated	5.322	1.29E-25
IL13	cytokine		0.883	1.06E-23
Alpha catenin	group	Inhibited	-7.925	2.56E-23
TCR	complex	Activated	4.57	2.24E-22
NFkB (complex)	complex	Activated	7.839	3.52E-21
STAT3	transcription regulator	Activated	5.128	4.32E-20
TREM1	transmembrane receptor	Activated	4.021	5.21E-17
FSH	complex		1.004	6.63E-17
IL4	cytokine	Activated	2.045	7.73E-17
STAT5A	transcription regulator		1.033	8.30E-17
IL1B	cytokine	Activated	6.76	8.42E-17
TGM2	enzyme	Activated	6.006	9.44E-17
ESR1	ligand-dependent nuclear receptor		1.779	2.38E-16
estrogen receptor	group	Inhibited	-5.867	5.55E-16
IL27	cytokine	Activated	3.987	8.21E-16
MAPK1	kinase	Inhibited	-2.686	1.16E-15
P38 MAPK	group	Activated	5.582	1.40E-15
TP63	transcription regulator	Activated	2.964	1.86E-15
NR3C1	ligand-dependent nuclear receptor		-0.469	6.97E-15
AHR	ligand-dependent nuclear receptor	Inhibited	-2.642	4.03E-14

ID3	transcription regulator		-0.459	7.18E-14
IL2	cytokine	Activated	4.64	9.53E-14
NUPR1	transcription regulator		1.327	1.28E-13
ID2	transcription regulator		-1.226	1.45E-13
CSF2	cytokine	Activated	7.497	2.02E-13
STAT1	transcription regulator	Activated	5.132	3.03E-13
CD44	enzyme	Activated	3.259	3.03E-13
PDGF BB	complex	Activated	5.416	4.63E-13
Cg	complex	Activated	5.27	5.57E-13
CD3	complex	Inhibited	-5.055	1.35E-12
IL1A	cytokine	Activated	5.907	1.77E-12
SP1	transcription regulator	Activated	3.045	2.66E-12
IFNA2	cytokine	Activated	5.188	4.15E-12
EP300	transcription regulator		0.401	4.23E-12
CREBBP	transcription regulator		-0.275	4.58E-12
IKBKB	kinase	Activated	5.678	6.03E-12
RELA	transcription regulator	Activated	5.225	6.64E-12
Lh	complex		0.531	7.96E-12
IFNL1	cytokine	Activated	5.927	8.67E-12
FGF2	growth factor	Activated	2.898	1.18E-11
Ifnar	group	Activated	5.913	1.23E-11
FAS	transmembrane receptor	Inhibited	-2.117	1.35E-11

Supplementary Table 7: Cytokine/Chemokine Genelist

Gene ID	Molecule Type
CCL11	Chemokine
CCL19	Chemokine
CCL21	Chemokine
CCL22	Chemokine
CCL28	Chemokine
CXCL12	Chemokine
CXCL16	Chemokine
XCL1	Chemokine
CCR2	Chemokine_Receptor
CCR4	Chemokine_Receptor
CCRL1	Chemokine_Receptor
CXCR4	Chemokine_Receptor
CXCR5	Chemokine_Receptor
CXCR7	Chemokine_Receptor
IL16	Cytokine
IL17B	Cytokine
IL1A	Cytokine
IL33	Cytokine
IL34	Cytokine
IL7	Cytokine
IL11RA	Cytokine_Receptor
IL17RE	Cytokine_Receptor
IL1RL2	Cytokine_Receptor
IL22RA1	Cytokine_Receptor
IL3RA	Cytokine_Receptor
IL4R	Cytokine_Receptor
CCR6	Chemokine_Receptor
IL18BP	Cytokine
IL1RL1	Cytokine_Receptor
IL10RB	Cytokine_Receptor
IL18R1	Cytokine_Receptor
IL6ST	Cytokine_Receptor
CCL2	Chemokine
CCR8	Chemokine_Receptor
IL18	Cytokine
IL1B	Cytokine
IL28RA	Cytokine_Receptor

XCL2	Chemokine
CCR3	Chemokine_Receptor
CCL23	Chemokine
CXCL6	Chemokine
IL23A	Cytokine
IL17RC	Cytokine_Receptor
CXCR1	Chemokine_Receptor
IL4I1	Cytokine
CXCR3	Chemokine_Receptor
CXCR6	Chemokine_Receptor
CCL5	Chemokine
CCR10	Chemokine_Receptor
IL10	Cytokine
CCL14	Chemokine
IL18RAP	Cytokine_Receptor
CXCL13	Chemokine
IL1F5	Cytokine
CCL18	Chemokine
IL2RG	Cytokine_Receptor
IL13RA2	Cytokine_Receptor
CCR1	Chemokine_Receptor
IL17RA	Cytokine_Receptor
IL10RA	Cytokine_Receptor
CCL13	Chemokine
IL11	Cytokine
CCL26	Chemokine
CCR5	Chemokine_Receptor
IL13RA1	Cytokine_Receptor
IL6R	Cytokine_Receptor
IL6	Cytokine
CXCL2	Chemokine
IL1R1	Cytokine_Receptor
CXCR2	Chemokine_Receptor
CCL20	Chemokine
IL8	Cytokine
IL7R	Cytokine_Receptor
CXCL14	Chemokine
IL12RB1	Cytokine_Receptor
IL17RB	Cytokine_Receptor

IL12A	Cytokine
CXCL9	Chemokine
CCL17	Chemokine
IL21R	Cytokine_Receptor
IL17D	Cytokine
IL17RD	Cytokine_Receptor
IL32	Cytokine
CCRL2	Chemokine_Receptor
CXCR2P1	Chemokine_Receptor
IL2RB	Cytokine_Receptor
IL24	Cytokine
CCL3L1	Chemokine
IL1R2	Cytokine_Receptor
CXCL11	Chemokine
CCR7	Chemokine_Receptor
CXCL1	Chemokine
CXCL3	Chemokine
IL2RA	Cytokine_Receptor
IL1RN	Cytokine_Receptor
CXCL10	Chemokine
CCL4L2	Chemokine
CCL8	Chemokine
IL27RA	Cytokine_Receptor
CXCL5	Chemokine
IL15	Cytokine
IL15RA	Cytokine_Receptor
IL1F9	Cytokine
CCL4	Chemokine
CCL3	Chemokine
IL20RB	Cytokine_Receptor
IL1RAP	Cytokine_Receptor
IL12RB2	Cytokine_Receptor
CXCL17	Chemokine
IL20RA	Cytokine_Receptor
IL9R	Cytokine_Receptor

Supplementary Table 9: Tumor Subtype Characteristics Summary

	Basal	Claudin-low	Luminal
Immune signatures	mixed	high	low
Immune suppressions	mixed	high	low
Predicted neoantigen burden	high	high	high
PPARG activity	low	low	high
cytokines/chemokines	mixed	high	low