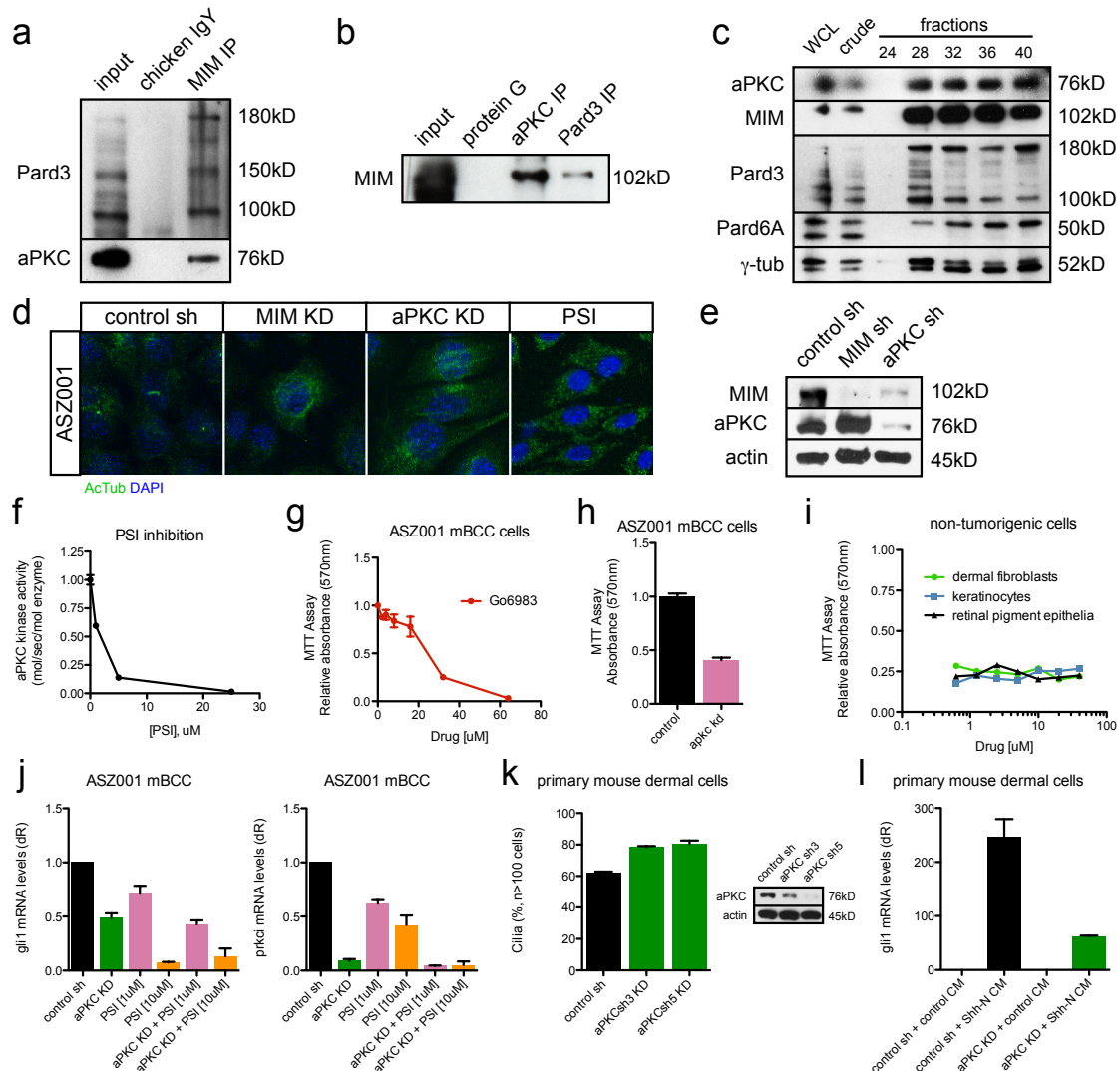
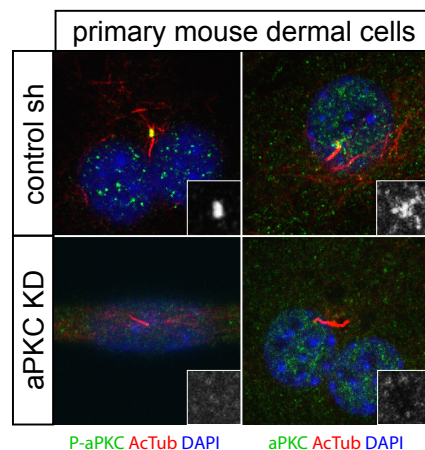
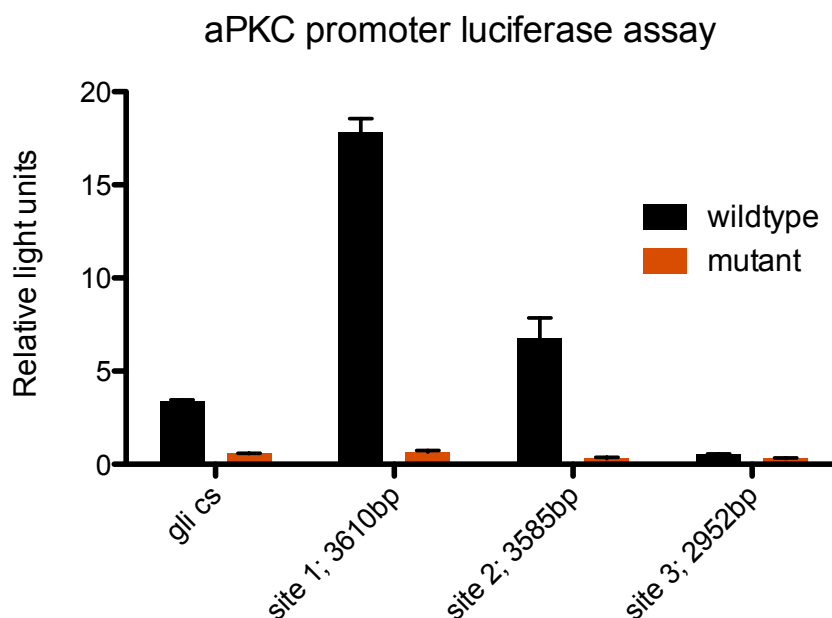




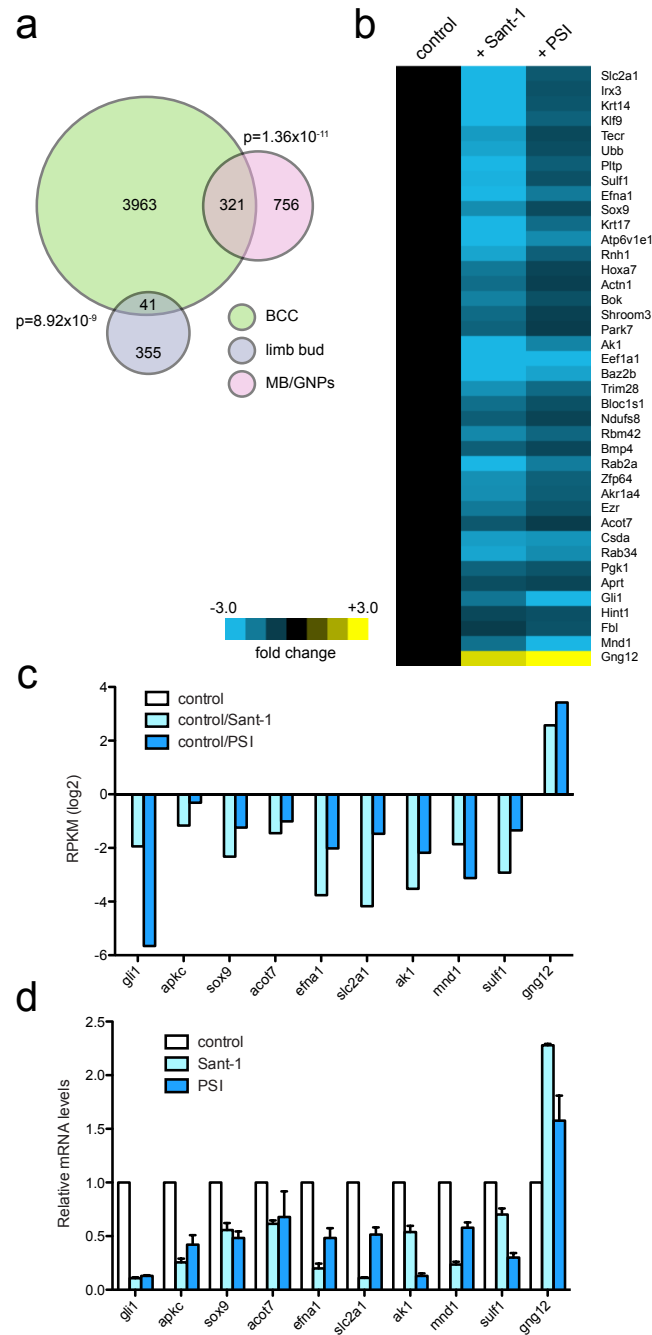
Supplementary Figure 1: aPKC alters BCC cell growth. **a, b**, Reciprocal immunoprecipitation of MIM-aPKC-Pard3 complexes from mouse dermal cells. **c**, Co-fractionation of purified centrosome fractions from mouse fibroblasts. WCL, whole cell lysate. Crude, unpurified centrosome lysate. γ -tub, γ -tubulin. **d**, Cilia (Actub) after shRNA knockdown of MIM, aPKC, or inhibition of aPKC in BCC cells (n=3). sh, short-hairpin. KD, knockdown. **e** aPKC or MIM protein levels compared to actin. **f**, PSI suppresses *in vitro* aPKC activity (n=3). **g**, Pan PKC inhibitor Go6983 suppresses BCC cell growth (n=3). **h**, aPKC knockdown reduces BCC cell growth (n=3). **i**, PSI does not alter cell proliferation of mouse dermal fibroblasts, mouse keratinocytes, and human retinal pigment epithelial cells (n=3). **j**, aPKC inhibition and shRNA knockdown do not amplify loss of Hh signaling (n=3). **k, l**, Hh signaling and ciliogenesis are separable in mouse dermal cells after aPKC shRNA (n=3). Error bars, s.e.m.



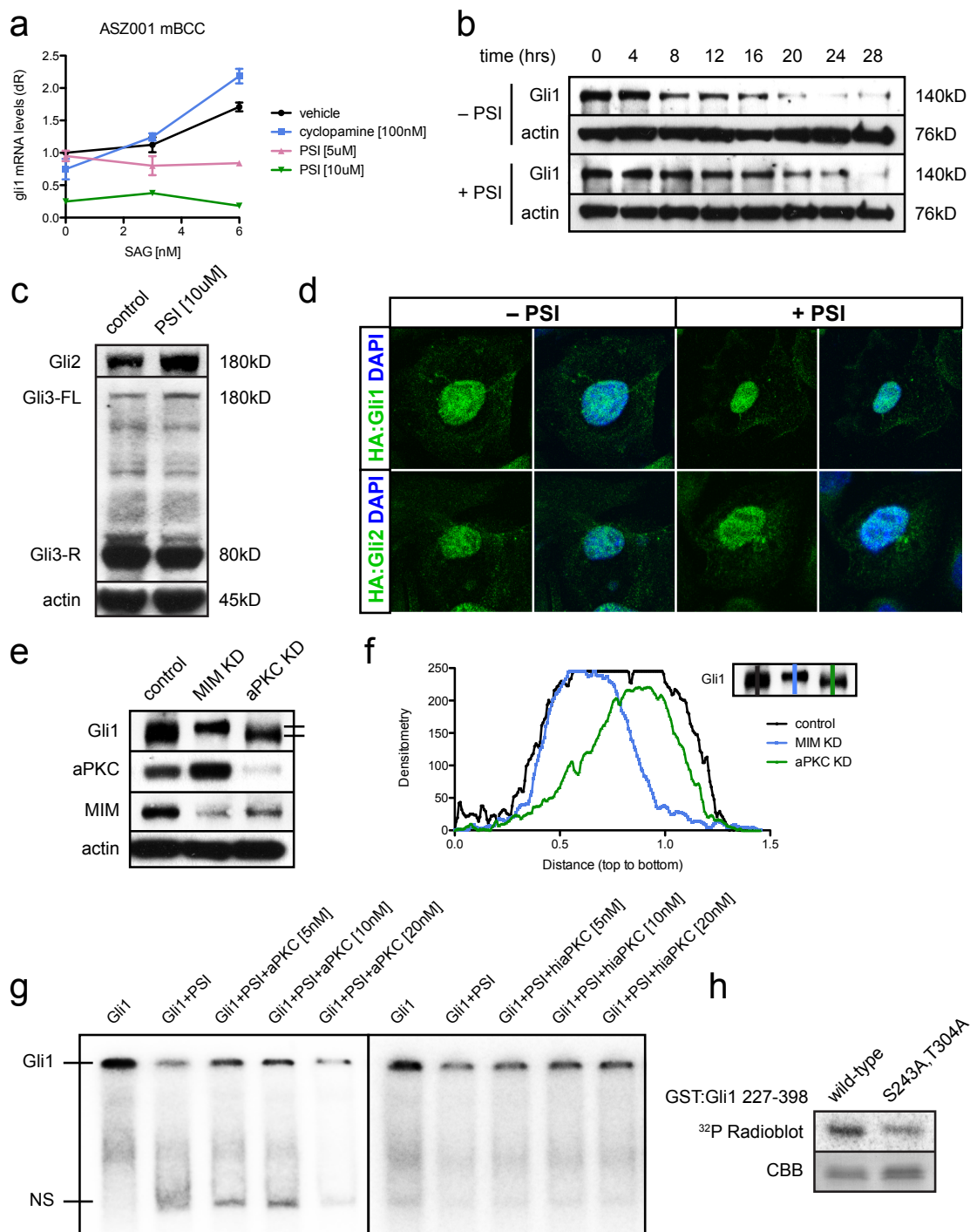
Supplementary Figure 2: aPKC localizes to the basal body. aPKC or P-aPKC found at the basal body of primary mouse dermal cells and immunoreactivity is reduced upon aPKC knockdown. Actub, acetylated tubulin.



Supplementary Figure 3: Functional Gli binding sites are found in the aPKC promoter. Luciferase assay of multimerized Gli binding sites or their mutants show two functional Gli binding sites within the aPKC promoter (n=4). Gli cs, consensus sequence. Error bars, s.e.m.

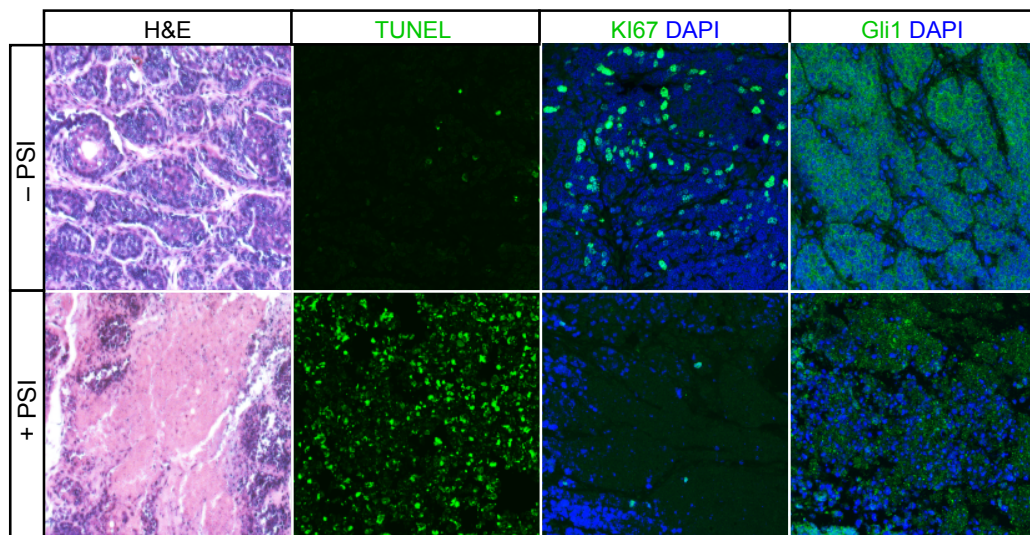


Supplementary Figure 4: aPKC inhibition affects Hh target genes. a, Venn diagram and **(b)** heatmap of commonly altered transcripts in both Sant-1 and PSI-treated samples compared to ChIP-Seq data sets from limb bud and medulloblastoma/GNPs. **c**, RPKM values and **(d)** subsequent validated transcript levels of commonly altered transcripts (n=3). Error bars, s.e.m.



Supplementary Figure 5: aPKC does not significantly affect Gli protein stability or processing. **a**, SAG does not rescue reduced Hh signaling from PSI-treated BCC cells (n=3). Error bars, s.e.m. **b**, PSI modestly stabilizes Gli1 protein levels in BCC cells. **c**, Gli processing is not altered with PSI treatment in primary mouse dermal cells where no

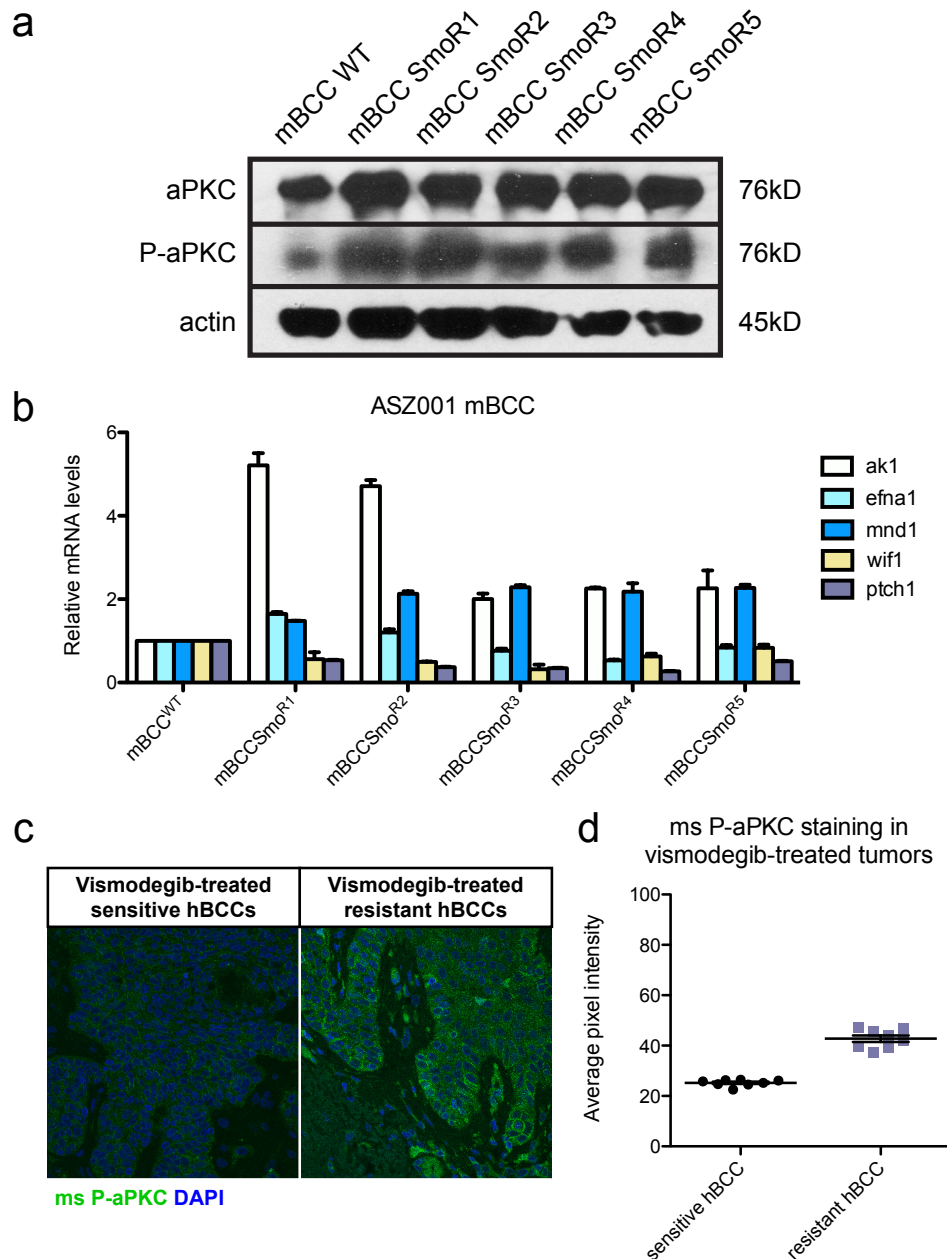
loss of cilia is observed. **d**, PSI does not alter transfected nuclear HA:Gli protein localization in BCC cells. **e**, Gli1 protein has altered electrophoretic mobility with knockdown of aPKC or MIM. **f**, Densitometry graph of Gli1 protein. **g**, Over phosphorylation of IVT human Gli1 by aPKC disrupts DNA binding whereas heat-inactivated aPKC does not rescue DNA-binding of PSI-treated Gli1. **h**, GST:Gli1 227-398^{S243A,T304A} accumulates less phosphorylation than wild-type protein when exposed to aPKC in an *in vitro* kinase assay.



Supplementary Figure 6: PSI disrupts tumor growth. BCC tumors lose classical palisades, with an increase in TUNEL-positive cells and a decrease in KI67-positive cells and Gli1 stain.

Value	DMSO	± SEM	PSI	± SEM
Glucose	257.9	28.05	255	38.19
AST	277.9	73.7	233.6	134.6
ALT	227.8	80.55	148.4	99.95
AlkPhos	270	42.17	247.8	17.46
GGT	0	0	0.714	0.63
Bilirubin	0	0	0.015	0.012
Chol	108.3	7.473	105.2	8.271
BUN	20.38	1.281	22.22	1.597
Creat	0.463	0.042	0.489	0.031
Ca	11.16	0.295	11.41	0.316
Phos	11.88	0.63	12.01	0.641
T.P.	5.5	0.138	5.689	0.247
Albumin	3.175	0.098	3.256	0.108
Globulin	2.325	0.088	2.433	0.17
Na	152.4	0.754	151	0.926
K	8.05	0.573	8.2	0.851
Cl	109.8	0.701	110.1	0.811
Co2	24.3	1.521	26.8	1.536
WBC	6.991	0.833	9.422	0.858
RBC	8.745	0.266	8.916	0.243
HGB	13.92	0.239	14.41	0.337
HCT	44.3	0.828	46.18	1.228
MCV	50.78	0.727	51.81	0.665
MCH	15.98	0.23	16.2	0.247
MCHC	31.45	0.192	31.26	0.297
Platelet	Adeq	Adeq	Adeq	Adeq
Neutrophil	14.75	4.858	17.22	3.09
Lymphocyte	77.25	5.195	72.89	2.988
Monocyte	6.125	1.156	9	1.067

Supplementary Figure 7: Topical PSI does not alter chemical or hematological parameters. Topical treatment of mice with DMSO (n=8) or 0.8mg/kg PSI dissolved in DMSO (n=9) results in no significant differences in blood parameters. Error bars, s.e.m.



Supplementary Figure 8: Vismodegib-resistant BCCs are positive for P-aPKC. **a**, Total and activated aPKC protein levels are enriched in Smo antagonist-resistant cell lines. **b**, Gli target gene transcript levels are differentially regulated in Smo-resistant BCC cells and follow *gli1* mRNA levels, *apkc* levels, or are generally suppressed (n=3). **c**, Activated P-aPKC is enriched in vismodegib-treated resistant human BCCs (n=2) compared to vismodegib-sensitive tumors (n=2) using a mouse monoclonal antibody. **d**, Average pixel intensity of mouse monoclonal P-aPKC antibody stains in vismodegib-treated human tumors. Error bars, s.e.m.

ChIP	forward oligo	reverse oligo	source
nanog	GGAAGAACCACTCCTACCAATACTCA	GTGTTTAAATTAATGTAGAGGCCTTCTG	Po et al, 2010
ptch1-1	ACAAAAGGAACGGAAAGTGT	AGCACGTTCTCCAGTTTAC	Vokes et al, 2007
ptch1-2	CCAGGCTCTCTCTAACAAGC	ACAACATTATCGCTGGGAAT	Vokes et al, 2007
rab34	CAAAAGCTCCATTCTCACAA	AGGAAACTGGGAGAACATCA	Vokes et al, 2007
nkx2-9	CTACCAAGCGTGCCTAAAGT	TTTATCCCAGGGAGCTAAAG	Vokes et al, 2007
hhip1	TAAAAGGGCACACTTGAAAA	AATTGCTGCAGACCCTAAAT	Vokes et al, 2007
actin	AGAAGGACTCCTATGTGGGTGA	ACTGACCTGGGTCTCTTTTC	Vokes et al, 2007
gapdh	ACAACCTTTGGCATTGAGGAA	GATGCAGGGATGATGTTCTG	IDT oligos
prkci-p1	TTGGTCCTGAGAGGCTGAAG	GTGGACAGCGATCATTGC	
prkci-p2	GGGTGCGAAGATGGCTCTCC	GTACCACTTCCTTGAATTGG	
qRTPCR			
prkci	AAGGAACGATTGGGTGTACCCCT	AAGGGTGGAACCACTGCTTTTGCT	IDT oligos
prkcz	ACATCATCACGGACAACCCTGACA	TGTGAGGCCTTGACAGACAGGAAA	IDT oligos
cdc42	GCAGGGCAAGAGGATTATGAC	TCTCAGGCACCCACTTTTC	IDT oligos
sulf1	TGCTGAACAGTCACCCTGATCCAA	ACCACATGACTTGGGTCTTCACCT	IDT oligos
mnd1	ATGACGGTATGGTTGACTGCGAGA	CCGGCCAACCTTGCTTTCTCAAT	IDT oligos
efna1	GTTTAACCAGCCCAACTGTGCCAT	AGGTCCGCACAGCTTGTTTCTTTG	IDT oligos
acot7	TGTGTATTTACGGCAGGAGCAGGA	AATGTCTCCGTTCTCCACTTGGT	IDT oligos
pard6a	CTGGGCTTCTACATTGAGGA	TGACAGTGACGATGAGGTTG	Realtimeprimers
sox9	CCAGCGTTTAACCTTCAAGA	TGACCATAACCTTTGAGGAA	Realtimeprimers
slc2a1	TGCCAAGCTAATCTGTAGGG	GAATGGGCGAATCCTAAAAT	Realtimeprimers
ak1	GGAGTGTGAGCTGCCATAGA	GGGAAGTCACTAGGGATGGA	Realtimeprimers
gng12	CTAAGCACCGGCAAATTAATA	GGTGGTTAGTGCCCATAGTG	Realtimeprimers

Supplementary Table 1.