Supplemental Figure 1. JNK1 kinase assay, p-JNK2 ELISA and JNK knock-down

(A) JNK1 kinase activities in UV treated *JNK1*$^{-/-}$ and *JNK2*$^{-/-}$ MEFs were assayed using a JNK1-specific antibody to immunoprecipitate JNK1 and GST-c-Jun as substrate. (B) p-JNK2 levels in UV treated *JNK1*$^{-/-}$ and *JNK2*$^{-/-}$ MEFs were measured by p-JNK2-specific ELISA assay. (C) Huh7 cell were infected with scramble, JNK1, JNK2 or JNK1/2 shRNA lentiviruses. JNK1 and JNK2 protein levels were detected by JNK1 or JNK2 immunoblots.

Supplemental Figure 2. Characterization of liver cancers and DNA-adducts in *JNK1*$^{-/-}$ mice

Apoptotic cells in liver and cancer tissues were analyzed by TUNEL assay in *JNK1*$^{-/-}$ (A) and *JNK2*$^{-/-}$ (B) mice. Quantifications of TUNEL positive cells are shown. (C) Vessels in liver cancers were analyzed by immunohistochemical staining of vWF. Arrowheads indicate vessels. (D) DNA adducts of O^6-Et-dG and O^2-Et-dT in liver genomic DNA were measured 0, 3 and 24 hours after DEN treatment by slot-blot.

Supplemental Figure 3. Molecular analyses of *JNK1*$^{-/-}$ and *JNK2*$^{-/-}$ liver cancers and regenerating livers

(A) Expressions of HGF, EGF, IGF1, TGFα and TGFβ were determined by qRT-PCR in *JNK1*$^{-/-}$ liver cancers. (B) TNFα, IL-1α, IL-1β, IL-6 and IL-12 levels were determined by ELISA using total protein lysates of *JNK1*$^{+/-}$ and *JNK1*$^{-/-}$ liver cancers. (C) Total JNK and p-ERK1/2, ERK1/2, p-AKT, AKT p-PTEN, p-GSK3β, p-Raf and p-PDK1 were analyzed by Western blots in *JNK1*$^{+/-}$ and *JNK1*$^{-/-}$ liver cancer tissues. β-actin was used as loading control. (D) JNK1/2 and c-Myc protein levels were determined by Western blot in *JNK2*$^{+/-}$

and *JNK2*$^{-/-}$ liver cancer tissues. Arrowhead indicates an unspecific band. (E) Expressions of HGF, EGF, IGF1, TGFα and TGFβ were determined by qRT-PCR in regenerating livers 12 hours after partial hepatectomy. (F). TNFα, IL-1α, IL-1β, IL-6 and IL-12 levels were determined by ELISA from total protein lysates of *JNK1*$^{+/-}$ and *JNK1*$^{-/-}$ regenerating livers 12 hours after partial hepatectomy.

Supplemental Figure 4. Sequence and structure analysis of JNK

(A) Phylogenetic analysis of JNK proteins from human (Hs.), mouse (Mm.), chicken (Gg.) and fruitfly (Dm.). The tree is built based on an alignment of proteins sequences of human JNKs (NP_620637.1, NP_002743.3, P53779.2), mouse JNKs (AAH53027.1, AAD22577.1, BAC76451.1), chicken JNKs (XP_001233169.1, NP_990426.1, XP_420551.2) and fruitfly JNK (AAB97094.1) using MAFFT (Katoh and Toh 2008). The phylogenetic tree was calculated applying the Jones-Taylor-Thornton method in the protdist program from the Phylogeny Inference Package (PHYLIP) (Felsenstein, J. 2005. version 3.6. Distributed by the author. Department of Genome Sciences, University of Washington, Seattle). The length of the edges between two JNKs indicates the phylogenetic distance between these two kinases. (B) Protein sequence alignment of human JNK1 and JNK2 shows the difference in amino acid residues 218-230 and 363-380. (C) Structure modeling based on the crystal structure of JNK3 (PDB: 1JNK) (Xie et al 1998) shows that amino acid residues 218-230 (green) and 363-380 (yellow) are surface located. Kinase activity socket is indicated as binding of ANP (red).

Katoh, K, Toh, H. 2008. Recent developments in the MAFFT multiple sequence alignment program. *Brief Bioinform*: doi:10.1093/bib/bbn013.

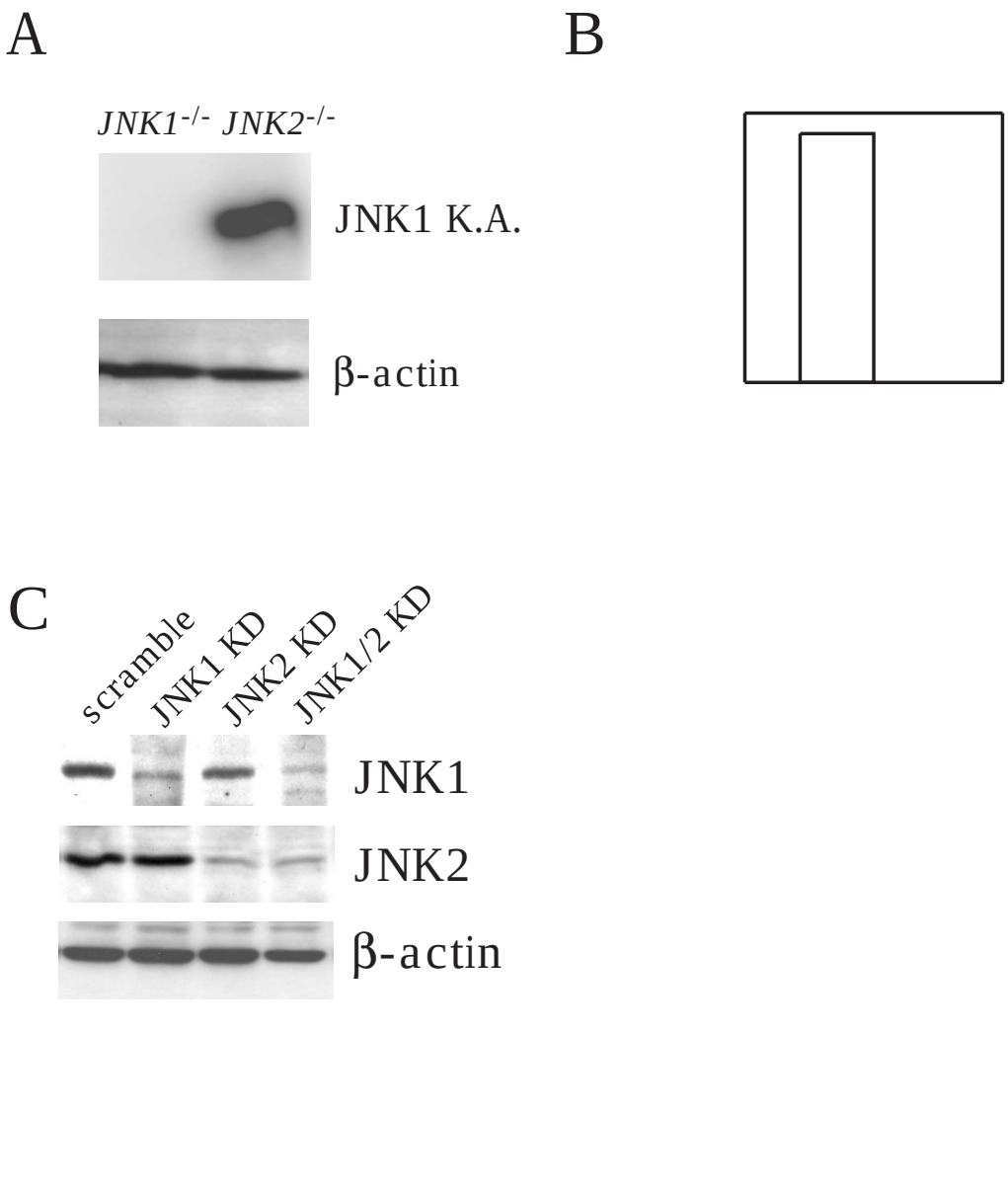
Xie, X., Gu, Y., Fox, T., Coll, J.T., Fleming, M.A., Markland, W., Caron, P.R., Wilson, K.P., Su, M.S. 1998. Crystal structure of JNK3: a kinase implicated in neuronal apoptosis. *Structure* 6(8): 983-991.

Supplemental Table 1: Semi-quantification of p-JNK staining on human HCC

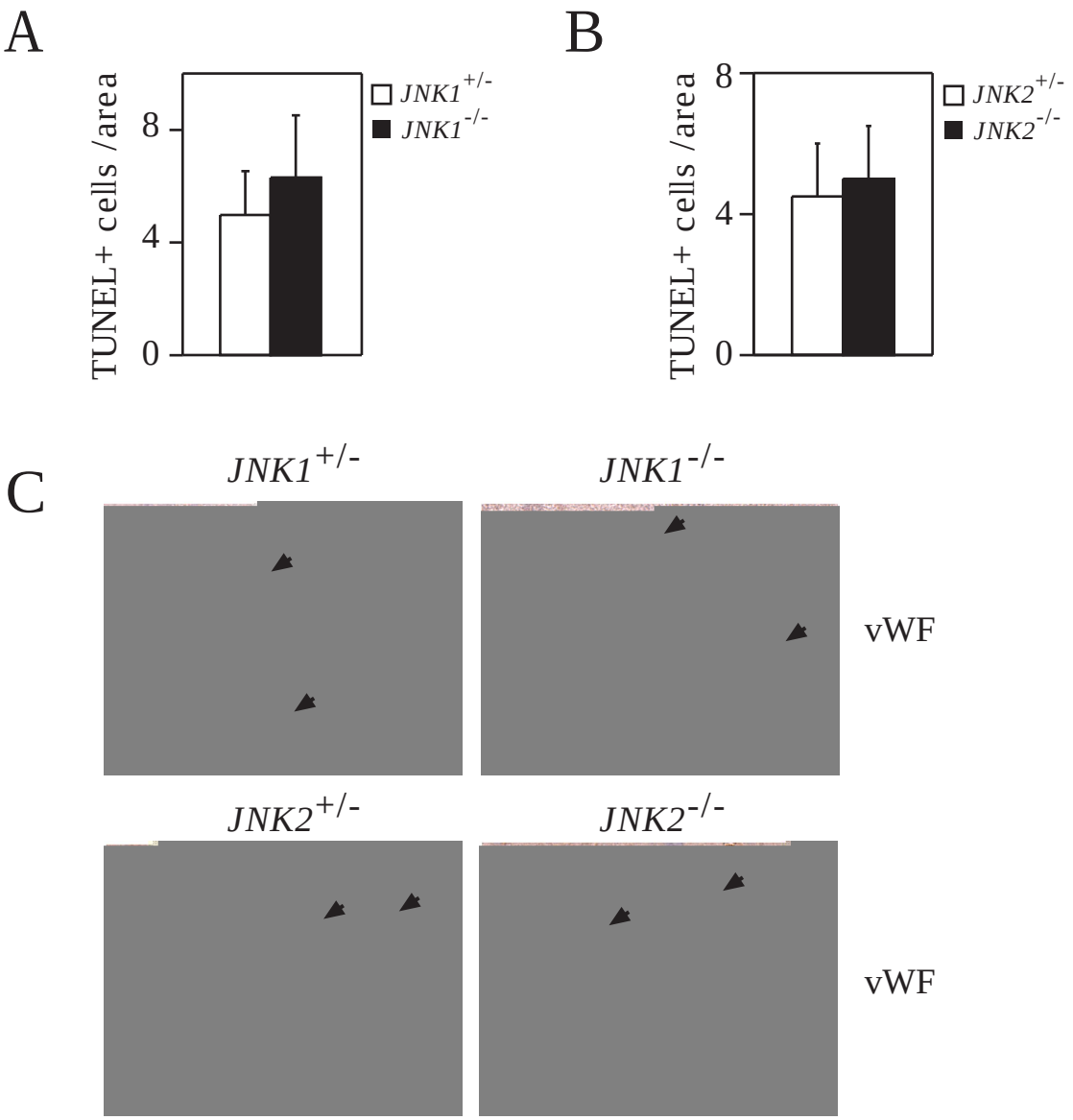
ID	HCC	Non-neoplastic
20004750	1	0
20004751	0	0
20006508	1	0
20006511	0	0
20006515	1	0
20006519	1	0
20006521	2	0
20006522	3	0
20006525	0	0
20006526	1	0
20006527	1	0
20006529	0	1
20006531	1	0
20006533	0	0
20006539	0	1
20006543	1	0
20006544	1	0
20006545	1	0
20006546	0	0
20006547	2	0
20006549	2	0
20006550	0	0
20006552	2	1
20006553	2	1
20006554	2	1
20006555	3	1
20006558	0	0
20006559	0	0
20006560	3	2
20006562	1	1
20006563	2	1
20006564	1	1
20006565	3	1
20006570	0	1
20006571	1	1
20006572	1	1
20006573	2	1
20006574	0	1
20006575	2	1
20006576	1	1
20006625	1	1

p-JNK staining has been performed on one tissue microarray, which guarantees identical reaction conditions as a basis for comparison of the semi-quantitative evaluation of staining intensities. Score 0: negative, 1: weakly positive, 2: moderately positive, 3: strongly positive for p-JNK staining.

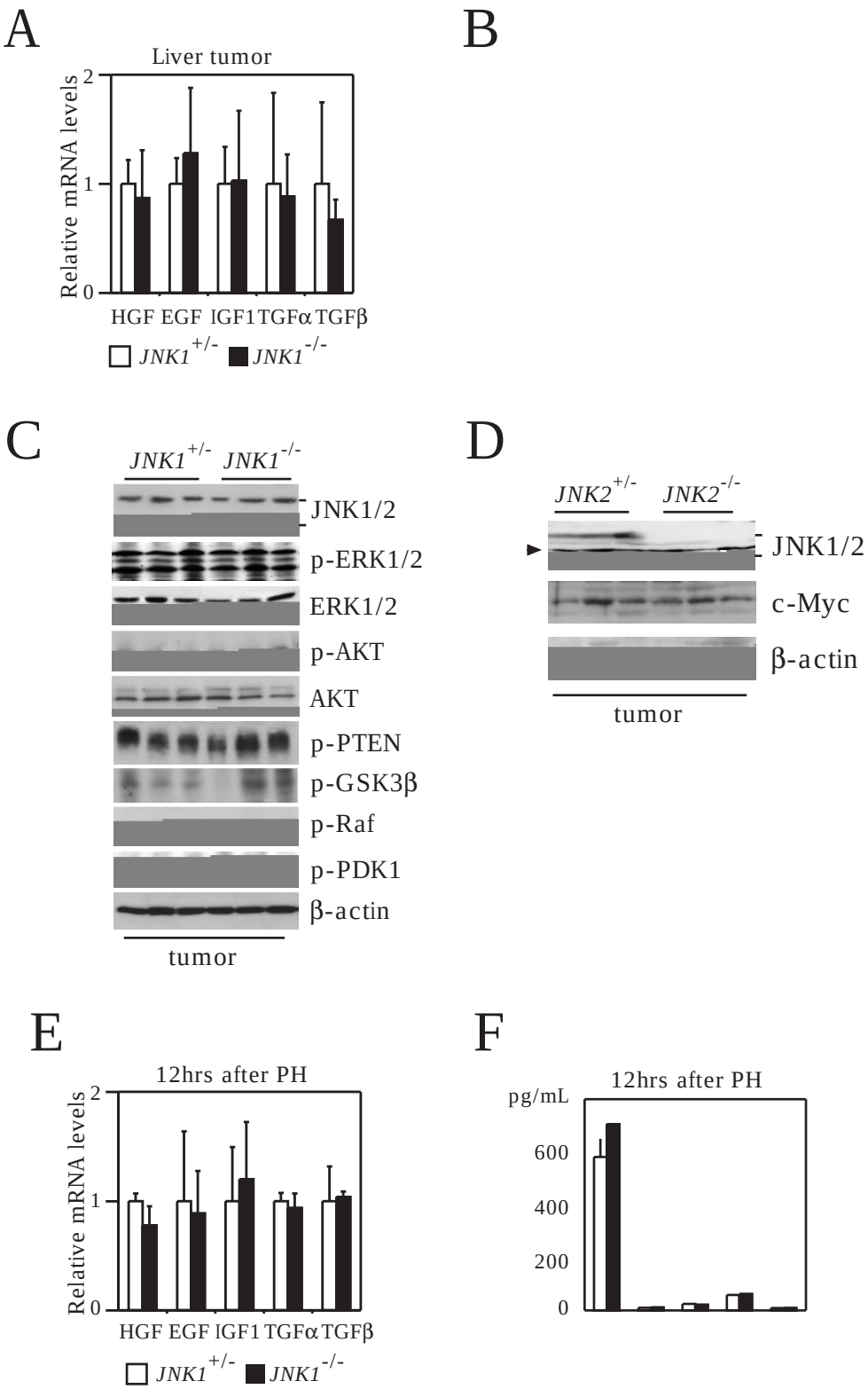
Supplemental Table 2. primers for qRT-PCR and chrom



Supplemental Figure 1 *Hui et al*

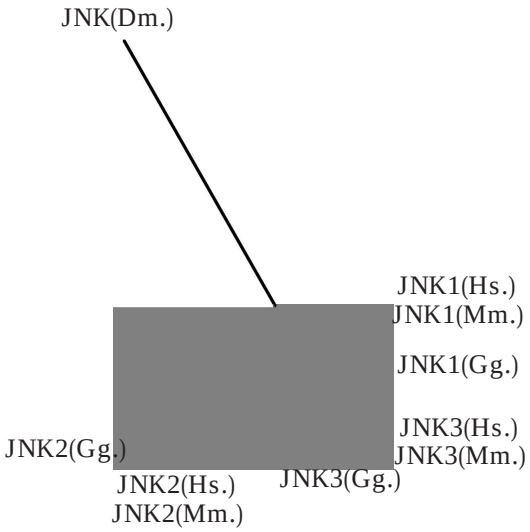


Supplemental Figure 2 *Hui et al*



Supplemental Figure 3 *Hui et al*

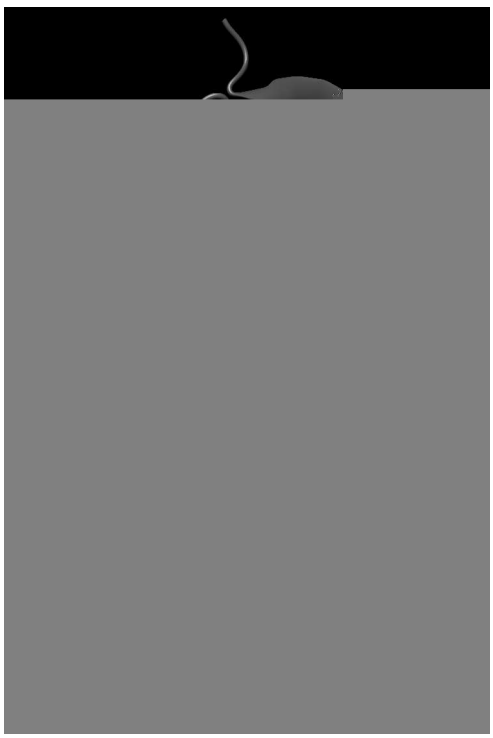
A



B

	218	363
JNK1(Hs.)	MVCHKILFPGRDY	LEERTKNGVIRGQPSPLA
JNK2(Hs.)	L.KGCVI.Q.T.H	W...S....VKD...DA.

C



Supplemental Figure 4 *Hui et al*