

Supplemental Data

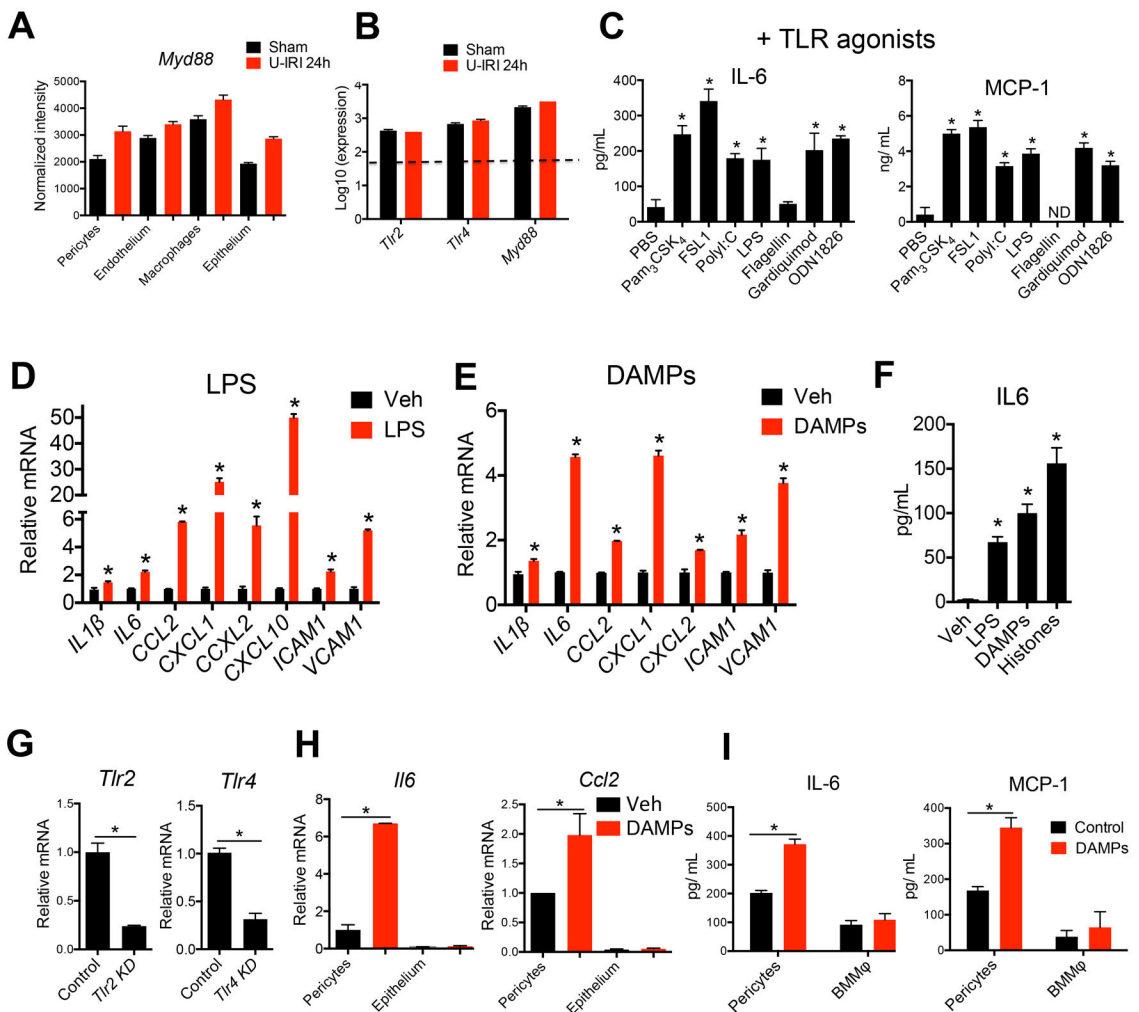
Pericyte MyD88 controls inflammatory and fibrotic responses to tissue injury

Irina A. Leaf^{1,2}, Shunsaku Nakagawa³, Bryce G. Johnson^{1,3}, Jin Joo Cha³, Kristen Mittelsteadt³, Kevin M. Guckian¹, Ivan G. Gomez^{1,3}, William A. Altemeier³, Jeremy S. Duffield^{1,3} *

1. Supplemental Figures
2. Supplemental Tables

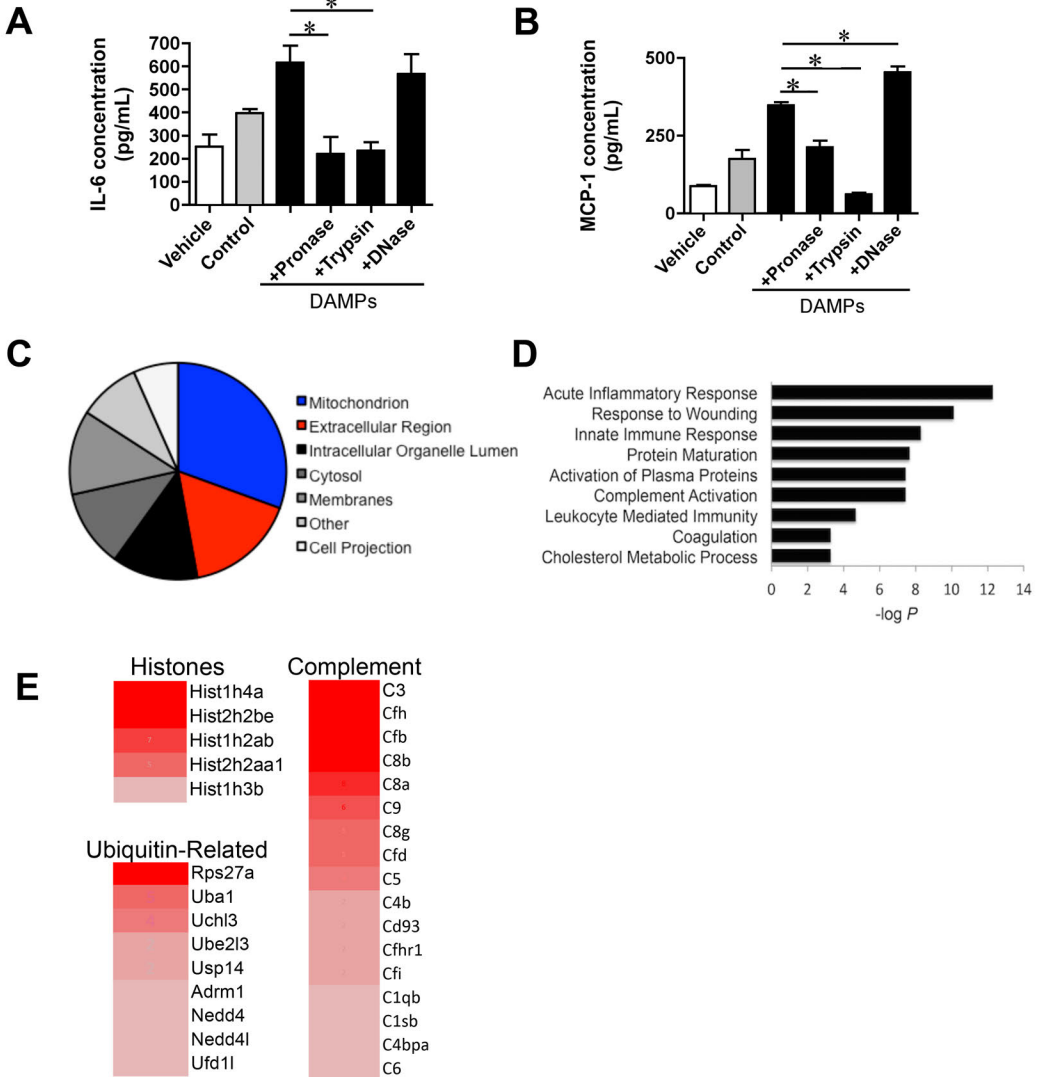
Supplementary Fig.1

Mouse and human pericytes respond to TLR ligands, kidney DAMPs and histones



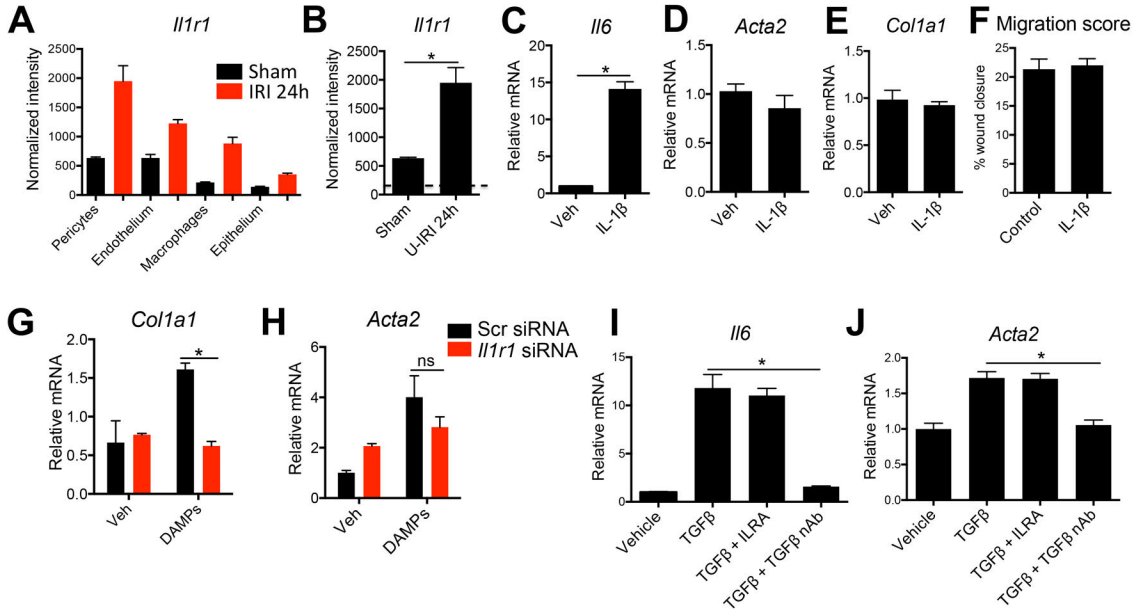
(A-B) MyD88 expression by 4 different cell types in the kidney in vivo (A) and TLR2, TLR4 and MyD88 expression in kidney pericytes (B) in vivo isolated by TRAP and detected by microarray. Dotted line designates the level of detection. (C) IL6 or MCP1 secretion by mouse kidney pericytes in response to different TLR ligands (D) Transcriptional response to LPS or (E) kidney DAMPs by human pericytes. (F) Secretion of IL-6 by human pericytes in response to LPS, kidney DAMPs or histones. (G) Transcript levels for TLR2 and TLR4 48h following specific or scrambled siRNA (H) Transcript levels for *Il6* and *Ccl2* in pericytes and primary mouse proximal epithelium in control and DAMPs activated conditions. (I) Secretion of IL-6 and MCP-1 by kidney pericytes or Bone marrow derived macrophages in culture in response to kidney DAMPs. (n = 3-5/group; **P* < 0.05; 2 tailed Student's t-test or ANOVA with Bonferroni's correction).

Supplementary Fig.2
Characterization of DAMPs



(A,B) Secretion of IL-6 and MCP-1 by kidney pericytes in culture in response to kidney DAMPs following pre-treatment with nucleases or proteinases. (C) Composition of kidney IRI DAMPs by cellular compartment. (D) Pathways enriched in kidney IRI DAMPs. (E) Most enriched protein groups (n = 3-6/group; * P < 0.05, one way ANOVA with Bonferroni's correction).

Supplementary Fig.3
Role of *Il1* & *Il1r1* in pericytes



(A-B) Expression of *Il1r1* in multiple cell types (A) and specifically in kidney pericytes (B) *in vivo* purified by TRAP and analyzed by microarray in healthy or 24h post-IRI kidneys. Dotted line designates the level of detection.

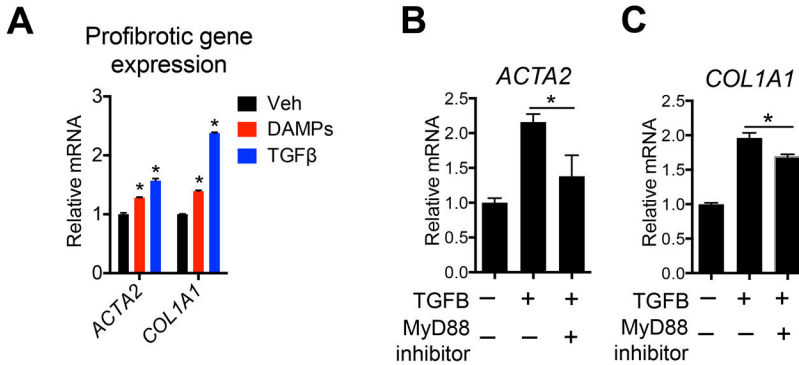
(C-E) Expression of *Il6*, *Acta2* and *Col1a1* in pericytes treated with IL-1 β for 24 hours.

(F) Migration of kidney pericytes in response to IL-1 β at 24 hours. (G-H) Impact of scrambled or *Il1r1*-specific siRNA on pericyte levels of *Col1a1* or *Acta2* transcripts 24 hours after treatment with either vehicle or DAMPs.

(I-J) Impact of IL1RA or anti-TGF β antibody on levels of *Il6* or *Acta2*, 24 hours after treatment with TGF β . (n = 3-5/group; *P < 0.05; 2 tailed Student's t-test or one way ANOVA with Bonferroni's correction).

Supplementary Fig.4

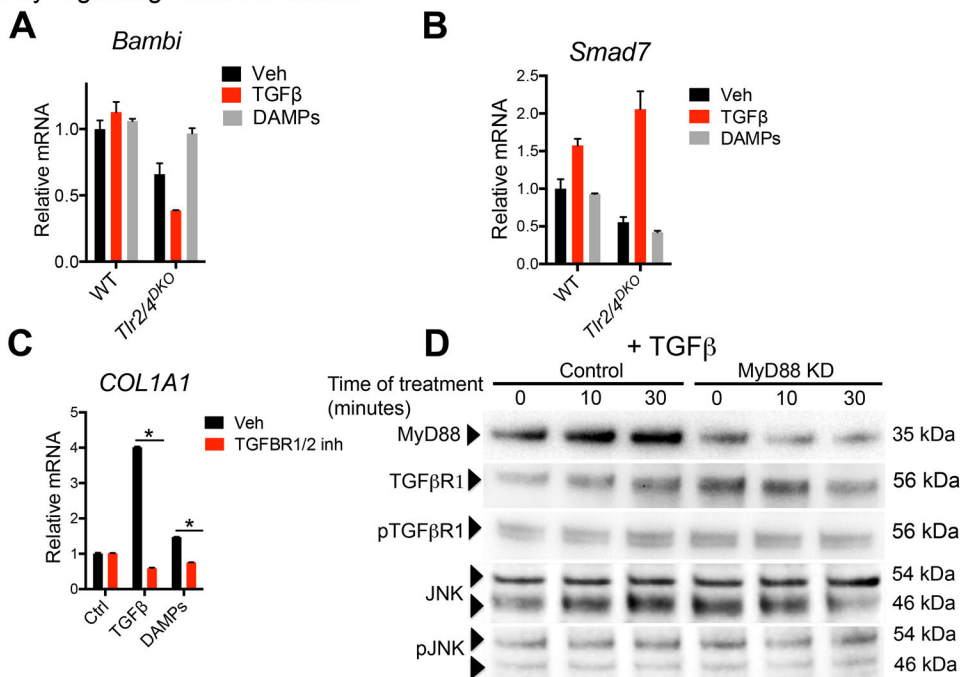
Human kidney pericytes respond to TGF β , kidney DAMPs or histones and this response is controlled by MYD88



(A) Expression of myofibroblast differentiation markers *ACTA2* and *COL1A1* in response to TGF β or kidney DAMPs. (B-C) Transcription of *ACTA2* and *COL1A1* following TGF β and MYD88 inhibitor treatments. (n = 3/group; * P < 0.05, 2 tailed Student's t-test or one way ANOVA with Bonferroni's correction).

Supplementary Fig. 5

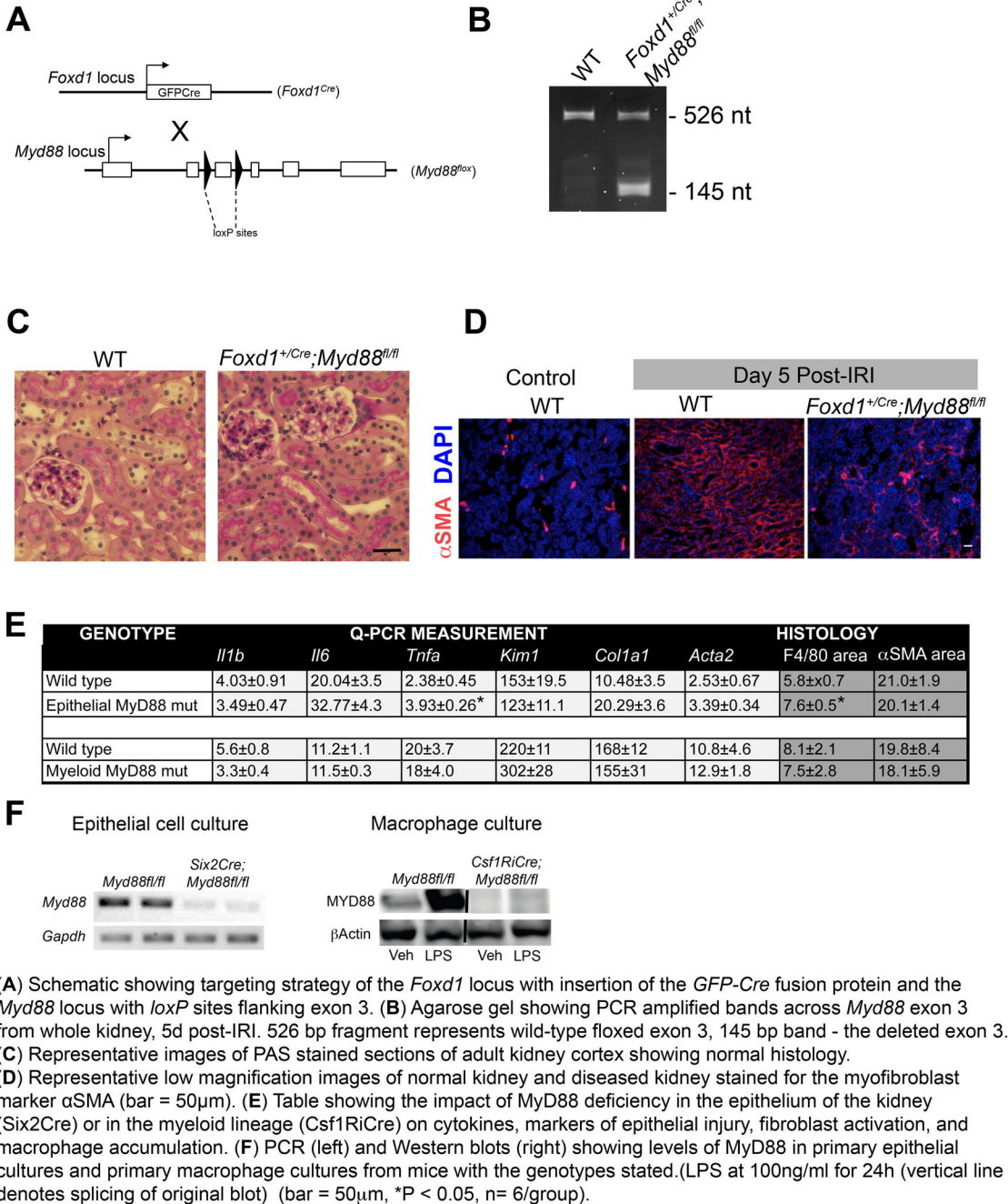
Crosstalk between TLR2/4 and MYD88 profibrotic signaling occurring at the receptor level but not by regulating *Bambi* or *Smad7*



(A-B) Transcription of *Bambi* and *Smad7* in mouse kidney pericytes stimulated with TGFβ or kidney DAMPs for 24 hours. (C) Effect of TGFβR1/2 inhibitor on TGFβ and DAMPs mediated expression of *COL1A1* in human pericytes (D) Western blotting with MyD88, TGFβR1, pTGFβR1, JNK or pJNK antibodies showing the effect of TGFβ treatment on control (scrambled siRNA) or MyD88 knock-down mouse kidney pericytes. (n = 3/group; * P < 0.05; 2-tailed Student's t-test).

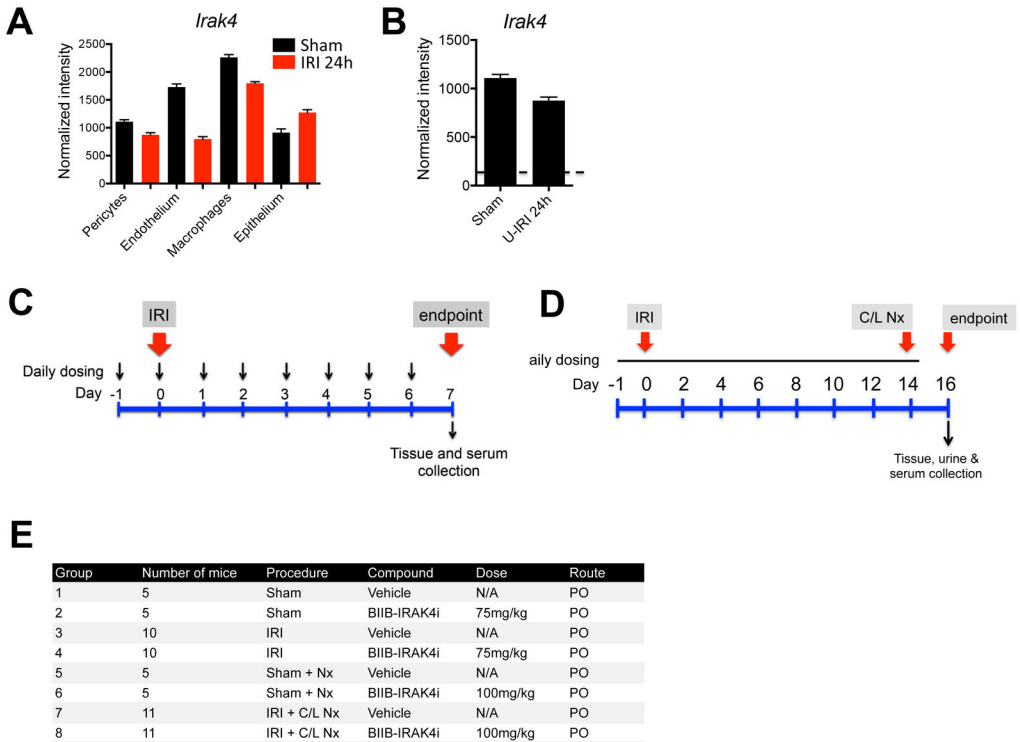
Supplementary Figure 6

Generation and characterization of the mouse strain with pericyte-specific deletion of MyD88



Supplementary Figure 7

Irak4 expression in the kidney and experiments to test inhibition by BIIB-IRAK4i *in vivo*.



(A-B) *Irak4* expression in pericytes, macrophages, endothelial and epithelial cells from healthy or 24h post-IRI kidneys detected by microarrays using TRAP. (B) Dotted line designates the level of detection. (C-E) *In vivo* study design (contralateral nephrectomy = C/L Nx) and experimental groups (groups 1-4, end point d7, and groups 5-8 end point d16) (n=3-11/group).

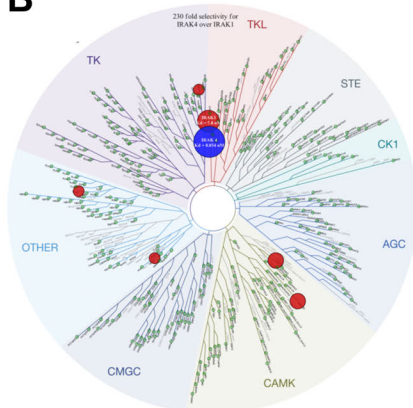
Supplementary Figure 8

Specificity and potency of the small molecule IRAK4 inhibitor BIIB-IRAK4i

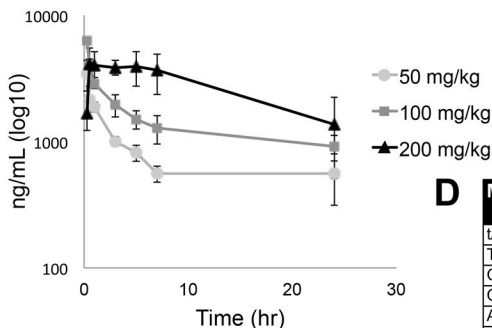
A

ASSAY	DESCRIPTION	BIIB-IRAK4i
IRAK4 biochemical IC50 - 1mM ATP	Biochemical potency	1 nM
IRAK1 biochemical IC50 - 10μM ATP	Biochemical potency	120 nM
IRAK4 Kd	Binding	0.034 nM
IRAK4 Kd	Binding	7.9 nM

B



C



D

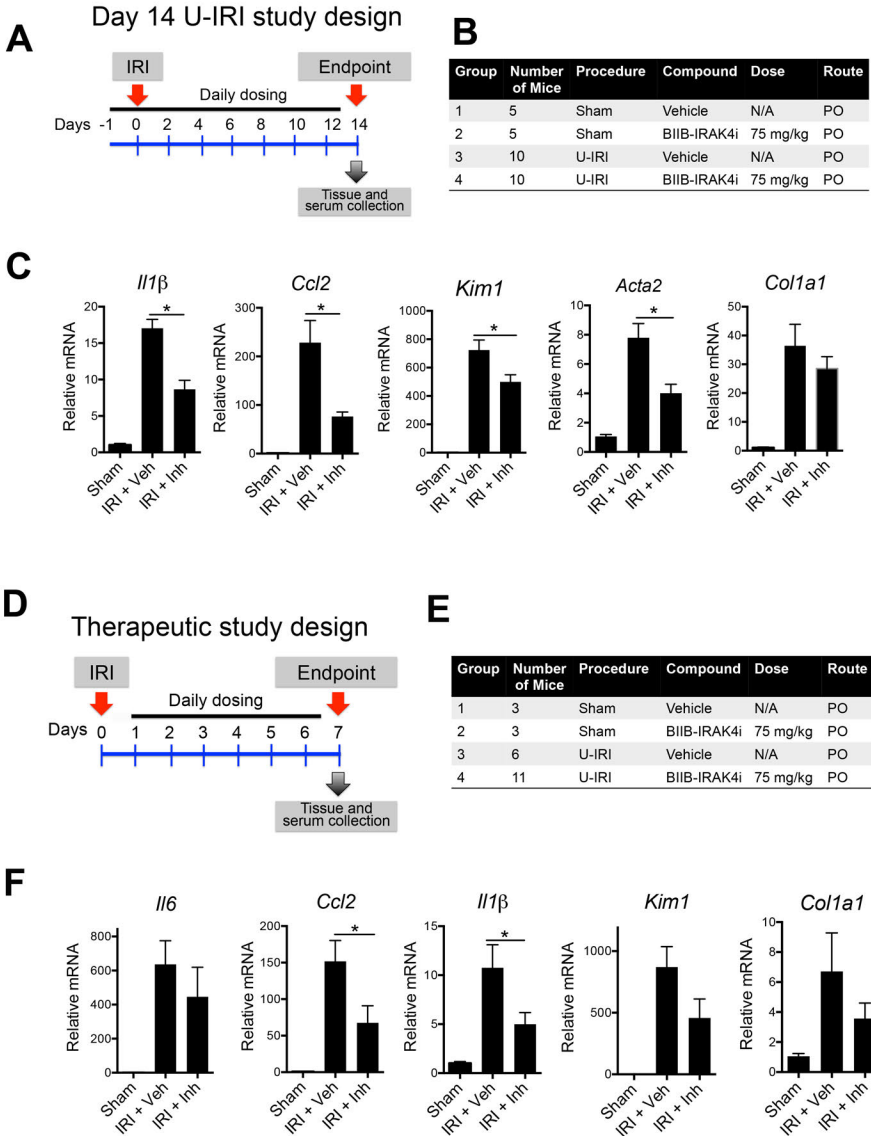
MEASUREMENT	UNITS	BIIB-IRAK4i DOSE		
		50 mg/ kg	100 mg/kg	200 mg/kg
t _{1/2}	hr	3.8	20.1	12.2
T _{max}	hr	0.25	0.25	0.5
C _{max}	ng/mL	3423	6240	4103
C _{max_d}	kg*ng/mL/mg	68	62	21
AUC _{clast}	hr*ng/mL	17708	33492	68818
AUC _{clast_D}	hr*kg*ng/mL/mg	354	335	344

(A) Results of an *in vitro* biochemical assay measuring inhibition of recombinant IRAK4 phosphorylation by BIIB-IRAK4i (IRAK4 was inhibited at an IC₅₀ of 1nM, IRAK1 was inhibited with an IC₅₀ 120 fold higher.) and a Biocore binding assay where the K_d for IRAK4 was 0.034nM but 230 fold higher for IRAK1.

(B) Phylogenetic tree of the human kinome showing 456 kinases that were evaluated using the DiscoverX kinase panel in inhibitory testing for BIIB-IRAK4i. Kinase groups are: TKL (tyrosine kinase like), TK (tyrosine kinase); STE (homologs of yeast sterile 7, 11), CK1 (Casein kinase 1), AGC (containing PKA, PKG, PKC families) CAMK (calcium/calmodulin dependent), CMGC (containing CDK, MAPK, GSK3, CLK families). BIIB-IRAK4i inhibited 7 kinases (shown as circles) by >90% at 1μM (S-Score(10) = 0.02). Circle size represents the amount of inhibition. BIIB-IRAK4i showed the highest inhibition of IRAK4 with a second ranked inhibition of IRAK1.

(C) Plasma concentration of BIIB-IRAK4i in mice given single oral dose of BIIB-IRAK4i as indicated at 50, 100 and 200 mg/ kg... (D) Pharmacokinetic parameters of BIIB-IRAK4i in male C57BL/6 mice following an oral dose of 50, 100, 200 mg/kg. The inhibitor is formulated in 50% PEG/Citric Acid. n=3 mice per group.

Supplementary Figure 9
Inhibition of disease progression by BIIB-IRAK4i *in vivo*.



(A) Experimental design for 14-day study of kidney U-IRI. (B) Experimental groups (C) Transcriptional levels of inflammatory (*Ccl2*, *Il1β*), tissue injury (*Kim1*) and fibrotic markers (*Acta2* and *Col1a1*) (D) Experimental design for 7-day U-IRI with therapeutic administration of IRAK4 inhibitor (E) Experimental groups. (F) Transcriptional levels of the inflammatory (*Il6*, *Ccl2*, *Il1β*) tissue injury (*Kim1*), and fibrotic markers (*Col1a1*) (* $P < 0.05$, $n=3-11$ /group, 2 tailed Student's t-test or one way ANOVA with Bonferroni's correction).

Supplemental Table 1

List of pathways enriched in human acute kidney injury

Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Bonferroni	Benjamini	FDR
GOTERM_BP_FAT	GO:0009611-response to wounding	22	21.57	7.50E-13	NFKBIZ, YWHAZ, CCL2, S100A8, CFB, LY96, CXCL2, S100A9, LYZ, ITGB3, C1S, SOD2, CD163, FOS, C1QB, ITGB6, SERPINA3, TFPI, SERPINA1, VCAN, CFI, PTX3	77	530	13528	7.292722	8.00E-10	8.00E-10	1.19E-09
GOTERM_BP_FAT	GO:0006954-inflammatory response	18	17.65	2.07E-12	NFKBIZ, YWHAZ, CCL2, S100A8, CFB, LY96, CXCL2, S100A9, LYZ, C1S, CD163, FOS, C1QB, ITGB6, SERPINA3, SERPINA1, CFI, PTX3	77	325	13528	9.73043	2.20E-09	1.10E-09	3.29E-09
GOTERM_BP_FAT	GO:0006952-defense response	21	20.59	1.05E-10	NFKBIZ, PTPRC, YWHAZ, CCL2, S100A8, CFB, LY96, S100A9, CXCL2, LYZ, C1S, ITGB1, CD163, FOS, C1QB, ITGB6, SERPINA3, MND, SERPINA1, CFI, PTX3	77	615	13528	5.999113	1.12E-07	3.72E-08	1.67E-07
GOTERM_BP_FAT	GO:0002526-acute inflammatory response	8	7.84	1.23E-06	C1QB, YWHAZ, CFB, SERPINA3, SERPINA1, C1S, CFI, CD163	77	98	13528	14.3419	0.001307	3.27E-04	0.00195
GOTERM_BP_FAT	GO:0006955-immune response	16	15.69	5.49E-06	PTPRC, YWHAZ, CCL2, CFB, LY96, CXCL2, C1S, HLA-DQA2, HLA-DQA1, C1QB, FCGR2C, FAS, CFI, FCGR3A, PTX3, FCGR3B	77	690	13528	4.073932	0.005841	0.001171	0.00875
GOTERM_BP_FAT	GO:0002252-immune effector process	8	7.84	9.90E-06	C1QB, PTPRC, YWHAZ, CFB, C1S, FAS, CFI, PTX3	77	134	13528	10.48885	0.010506	0.001759	0.01577
GOTERM_BP_FAT	GO:0007229-integrin-mediated signaling pathway	6	5.88	4.46E-05	ADAM10, ITGB6, ADAMTS1, ITGB3, ITGB1, ADAM9	77	70	13528	15.059	0.04647	0.006775	0.07102

Supplemental Table 2

List of pathways enriched in myofibroblasts

Category	Term	Count	%	PValue	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Bonferroni	Benjamini	FDR
KEGG_PATHWAY	mmu03030:DNA replication	23	1.04	1.53E-12	LIG1, POLA1, MCM2, MCM3, RNASEH2A, RNASEH2B, MCM5, RNASEH2C, RPA3, MCM6, POLD3, PRIM1, RFC5, RPA2, POLD4, RFC3, POLE4, RFC4, POLE2, RFC2, POLE3, PRIM2, FEN1	695	35	5738	5.42545	2.71E-10	2.71E-10	1.88E-09
KEGG_PATHWAY	mmu04110:Cell cycle	40	1.8	1.80E-08	DBF4, TGFB3, TTK, CHEK1, SFN, CHEK2, ZBTB17, TGFB1, TGFB2, CCNE2, CCNE1, CDC45, CDKN2C, BUB1, CCNA2, MYC, CDC7, TRP53, CDC6, CDK1, RBL1, YWHAB, SKP2, CDC20, MCM2, CDC26, CDC25C, MCM3, CDC27, CDK2, CDC25A, MCM5, MCM6, CCNB1, CDKN1A, CCNB2, PLK1, BUB1B, ANA	695	128	5738	2.58004	3.18E-06	1.59E-06	2.21E-05
KEGG_PATHWAY	mmu00240:Pyrimidine metabolism	31	1.4	4.44E-07	POLR2H, POLR2F, POLR2L, DTYMK, POLA1, DCK, CAD, POLR2D, TK1, PRIM1, TYMS, POLE4, POLE2, POLE3, NT5M, PRIM2, UCK2, POLR3K, POLR1D, POLR3GL, POLR3C, POLR3D, POLD3, NME4, NME5, POLD4, RRM2, RRM1, TXNRD2, UCKL1, DUT	695	96	5738	2.66604	7.86E-05	2.62E-05	5.45E-04
KEGG_PATHWAY	mmu00230:Purine metabolism	41	1.85	2.31E-06	ADCY3, POLR2H, POLR2F, GDA, ENPP1, ADCY7, POLR2L, DCK, POLA1, POLR2D, ADA, PRIM1, POLE4, POLE2, PDE1B, NT5M, POLE3, PRIM2, GUCY1A3, ENTPD2, IMPDH1, POLR3K, POLR1D, NUDT5, AK2, AK5, POLR3GL, GMPR, POLR3C, GART, POLR3D, APRT, POLD3, NME4, NME5, POLD4, PDE7B	695	157	5738	2.15606	4.08E-04	1.02E-04	0.0028
KEGG_PATHWAY	mmu04623:Cytosolic DNA-sensing pathway	19	0.86	4.58E-05	IL6, POLR3K, LOC100044068, POLR1D, POLR3GL, IL33, CCL5, POLR3C, AIM2, POLR3D, IFI202B, IKBKE, TMEM173, IRF7, PYCARD, RIPK3, CASP1, ZBP1, ADAR	695	55	5738	2.85211	0.0080806	0.001621	0.0563
KEGG_PATHWAY	mmu04060:Cytokine-cytokine receptor interaction	50	2.25	1.82E-04	OSMR, IL6ST, LEPR, TGFB3, IL17RA, TGFB1, IL11, TGFB2, CXCR4, CLCF1, CSF2RB, IL13RA1, CSF2RA, CD40, INHBB, INHBA, IFNAR2, CCR5, TNFSF13B, CX3CR1, PDGFRA, NGFR, ACVR1, IL1R2, TNFRSF21, IL1R1, CCL2, CXCL5, CSF2RB2, TNFRSF12A, CSF1, CRLF2, IL4RA, CCL9, CCL8	695	244	5738	1.69183	0.0316503	0.005346	0.2229
KEGG_PATHWAY	mmu04062:Chemokine signaling pathway	40	1.8	2.08E-04	ADCY3, CCL2, ADCY7, CXCL5, BCAR1, CCL9, CCL8, PF4, CX3CL1, CCL5, CCL6, DOCK2, RAC2, CXCR4, GNG2, SHC1, PIK3R5, PLCB1, AKT3, PIK3R2, GNG7, AKT2, NCF1, HCK, PIK3CD, STAT3, PRKCB, HRAS1, CCL17, NRAS, CCL12, GNGT2, CCR5, CXCL14, CX3CR1, GRK6, JAK2, GNB4, RAP1	695	182	5738	1.81453	0.036086	0.005237	0.2547
KEGG_PATHWAY	mmu04512:ECM-receptor interaction	23	1.04	2.41E-04	COL3A1, ITGA4, ITGB3, COL5A3, COL5A2, COL5A1, HMMR, ITGA9, SDC1, CD44, GP1BB, ITGA5, ITGAV, COL6A2, COL1A2, COL1A1, THBS1, THBS2, COL11A1, THBS3, SPP1, THBS4, FN1	695	83	5738	2.28784	0.0417313	0.005314	0.2954
KEGG_PATHWAY	mmu05221:Acute myeloid leukemia	18	0.81	2.68E-04	TCF7, PPARD, PIK3CD, RUNX1T1, PML, LEF1, RPS6KB2, RPS6KB1, STAT3, HRAS1, NRAS, EIF4EBP1, PIK3R5, RUNX1, MYC, AKT3, AKT2, PIK3R2	695	57	5738	2.60719	0.0462796	0.005251	0.3283
KEGG_PATHWAY	mmu03420:Nucleotide excision repair	15	0.68	3.39E-04	RAD23B, LIG1, RPA3, POLD3, RFC5, POLD4, XPA, ERCC8, RPA2, POLE4, RFC3, RFC4, POLE2, RFC2, POLE3	695	43	5738	2.88004	0.0582855	0.005987	0.4159
KEGG_PATHWAY	mmu04620:Toll-like receptor signaling pathway	25	1.13	5.45E-04	TLR1, CCL5, MAP3K7, FOS, MYD88, CASP8, TICAM1, PIK3R5, LBP, AKT3, AKT2, SPP1, PIK3R2, IL6, MAP2K4, PIK3CD, FADD, MAPK11, CD40, IFNAR2, IKBKE, IRF5, MAPK13, IRF7, CD14	695	99	5738	2.08488	0.0920157	0.008737	0.6676
KEGG_PATHWAY	mmu03430:Mismatch repair	10	0.45	6.06E-04	POLD3, RFC5, RPA2, POLD4, RFC3, RFC4, RFC2, LIG1, PMS2, RPA3	695	22	5738	3.75278	0.1016596	0.008894	0.7412
KEGG_PATHWAY	mmu03440:Homologous recombination	11	0.5	7.69E-04	POLD3, RPA2, POLD4, XRCC3, MRE11A, EME1, TOP3A, RAD54B, RAD54L, RAD51, RPA3	695	27	5738	3.3636	0.1272366	0.010414	0.94
KEGG_PATHWAY	mmu04914:Progesterone-mediated oocyte maturation	22	0.99	9.15E-04	ADCY3, CDK1, ADCY7, PIK3CD, MAPK11, CDC26, CDC25C, CDC27, CDC25A, CDK2, PGR, CCNB1, CCNB2, PLK1, MAPK13, BUB1, PIK3R5, ANAPC7, CCNA2, AKT3, AKT2, PIK3R2	695	85	5738	2.13688	0.1496295	0.011511	1.1185
KEGG_PATHWAY	mmu04662:B cell receptor signaling pathway	21	0.95	0.001	BCL10, PIK3CD, CD72, HRAS1, PRKCB, FOS, NRAS, RAC2, FCGR2B, DAPP1, LILRB3, PPP3CB, PPP3CC, PIK3AP1, PIK3R5, NFATC4, NFATC2, AKT3, AKT2, PIK3R2, NFATC1	695	80	5738	2.16723	0.1662108	0.012045	1.2535
KEGG_PATHWAY	mmu04210:Apoptosis	22	0.99	0.0013	TRP53, IRAK2, IL1R1, CSF2RB2, PIK3CD, FADD, BIRC3, TRADD, CASP6, MYD88, PRKAR1B, CASP8, PRKAR1A, CASP12, PPP3CB, CSF2RB, PPP3CC, PIK3R5, AKT3, IL3RA, AKT2, PIK3R2	695	87	5738	2.08775	0.2003386	0.013876	1.5395
KEGG_PATHWAY	mmu03410:Base excision repair	13	0.59	0.002	UNG, LIG1, NEIL3, NEIL1, POLD3, POLD4, MPG, POLE4, POLE2, POLE3, PARP3, APEX1, FEN1	695	40	5738	2.68324	0.2974776	0.020555	2.4204
KEGG_PATHWAY	mmu04115:p53 signaling pathway	18	0.81	0.0028	TRP53, STEAP3, CDK1, RPRM, CHEK1, CHEK2, SFN, CDK2, CCNE2, CCNB1, CCNE1, CDKN1A, CCNB2, RRM2, SERPINE1, CASP8, GADD45B, THBS1	695	69	5738	2.15377	0.3942314	0.027463	3.4187
KEGG_PATHWAY	mmu05200:Pathways in cancer	57	2.57	0.0028	PPARD, FGF7, MMP9, TGFB3, FGF11, NFKB2, FGF12, GLI2, MMP2, TGFB1, TGFB2, CCNE2, CCNE1, CUL2, FOS, WNT4, CASP8, RALA, MYC, AKT3, CSF2RA, AKT2, PIK3CD, SKP2, RUNX1T1, LEF1, FADD, DAPK3, CDK2, PRKCB, HRAS1, RAD51, PDGFRA, WNT5A, CKS1B, PML, TPMS3, RAC2, ITGAV	695	323	5738	1.45696	0.3962543	0.026208	3.4411
KEGG_PATHWAY	mmu04370:VEGF signaling pathway	19	0.86	0.0034	PIK3CD, SPHK1, MAPKAPK3, MAPK11, SRC, HRAS1, PRKCB, NRAS, RAC2, MAPK13, PPP3CB, PPP3CC, PIK3R5, NFATC4, NFATC2, AKT3, AKT2, PIK3R2, NFATC1	695	76	5738	2.06403	0.4551047	0.029902	4.1259
KEGG_PATHWAY	mmu04350:TGF-beta signaling pathway	20	0.9	0.0069	RBL1, SMAD5, FST, TGFB3, RPS6KB2, RPS6KB1, SMAD1, TGFB1, TGFB2, INHBB, INHBA, ID3, SMURF1, BMPR1B, THBS1, MYC, THBS2, THBS3, ACVR1, THBS4	695	87	5738	1.89796	0.7062682	0.056669	8.1501

Supplemental Table 2 (continued)

KEGG_PATHWAY	mmu04510:Focal adhesion	37	1.67	0.0073	CAV3, TLN1, BCAR1, COL3A1, ITGB3, SRC, RAC2, ITGAV, COL6A2, SHC1, PIK3R5, ZYX, THBS1, COL11A1, THBS2, THBS3, AKT3, PIK3R2, FN1, SPP1, AKT2, THBS4, PIK3CD, ITGA4, HGF, COL5A3, BIRC3, COL5A2, COL5A1, PRKCB, HRAS1, ITGA9, ITGA5, PDGFRA, COL1A2, RAP1B, COL1A1	695	198	5738	1.54281	0.7249143	0.056979	8.5672
KEGG_PATHWAY	mmu04010:MAPK signaling pathway	46	2.07	0.0104	IL1R2, IL1R1, FGF7, TGFB3, FGF11, MAPKAPK3, CACNB3, NFKB2, FGF12, SRF, TGFB1, TGFB2, MAP3K7, FOS, RAC2, PPP3CB, PPP3CC, NFATC4, NFATC2, MYC, AKT3, AKT2, TRP53, CACNA2D1, NTF5, CACNG8, PTPN5, MAP2K4, RELB, NR4A1, MAPK11, STK3, PRKCB, HRAS1, NRAS, MAP4K4, D	695	265	5738	1.43314	0.8421952	0.07714	12.026
KEGG_PATHWAY	mmu04120:Ubiquitin mediated proteolysis	27	1.22	0.0111	SYVN1, PML, SAE1, UBE2R2, FANCL, ERCC8, CUL2, UBE2D3, MGRN1, UBE2D1, UBE2A, SOCS3, SKP2, UBE2J1, UBE2F, UBE2L6, CDC20, BIRC3, UBE2C, CDC26, UBE2B, CDC27, BRCA1, DET1, SMURF1, ANAPC7, UBE2S	695	136	5738	1.63908	0.8614384	0.079052	12.816
KEGG_PATHWAY	mmu03020:RNA polymerase	9	0.41	0.0119	POLR2H, POLR2F, POLR3K, POLR2L, POLR1D, POLR3GL, POLR3C, POLR2D, POLR3D	695	27	5738	2.75204	0.8804629	0.081456	13.705
KEGG_PATHWAY	mmu04666:Fc gamma R-mediated phagocytosis	21	0.95	0.0122	PLD2, LIMK2, MARCKSL1, NCF1, HCK, WASF1, PIK3CD, SPHK1, RPS6KB2, RPS6KB1, FCGR1, PRKCB, DOCK2, RAC2, FCGR2B, GAB2, PIK3R5, AKT3, DNM1, AKT2, BRCA1, DET1, SMURF1	695	98	5738	1.76917	0.8854909	0.079971	13.962
KEGG_PATHWAY	mmu04130:SNARE interactions in vesicular transport	11	0.5	0.0126	STX6, SNAP29, STX1A, STX2, BNIPI1, BET1, GOSR2, SNAP23, GOSR1, STX11, VTI1A	695	38	5738	2.38993	0.8932155	0.079511	14.378
KEGG_PATHWAY	mmu00520:Amino sugar and nucleotide sugar metabolism	12	0.54	0.0134	CYB5R3, GMPPB, RENBP, NANS, GFPT1, GNPAT1, GFPT2, PGM1, NPL, HK2, NANP, FMM1	695	44	5738	2.25167	0.9087217	0.081942	15.306
KEGG_PATHWAY	mmu04630:Jak-STAT signaling pathway	29	1.31	0.0141	OSMR, CSF2RB2, IL6ST, LEPR, STAM2, CRLF2, IL4RA, CNTRF, IL11, LIF, CLCF1, CSF2RB, IL2RG, PIK3R5, IL13RA1, MYC, AKT3, CSF2RA, PIK3R2, AKT2, IL6, SOCS2, SOCS3, PIK3CD, STAT3, IFNAR2, JAK2, JAK3, IL3RA	695	152	5738	1.57518	0.9193343	0.083147	16.029
KEGG_PATHWAY	mmu04114:Oocyte meiosis	23	1.04	0.0184	ADCY3, CDK1, ADCY7, SGOL1, YWHAB, AURKA, CDC20, CDC26, CDC25C, CDC27, CDK2, CCNE2, PGR, CCNB1, CCNE1, CCNB2, PLK1, PPP3CB, BUB1, FBXO5, PPP3CC, ANAPC7, CAMK2A	695	115	5738	1.65122	0.9627903	0.103903	20.419
KEGG_PATHWAY	mmu04310:Wnt signaling pathway	28	1.26	0.0193	WNT5A, NKD1, PPARD, NKD2, MMP7, MAP3K7, WNT4, CSNK2A1, RAC2, PPP3CB, PPP3CC, NFATC4, PLCB1, NFATC2, CAMK2A, MYC, FOXL1, NFATC1, TRP53, TCF7, LEF1, FZD3, PRKCB, DKK2, CTNBP1, SFRP1, CSNK1E, LRP5	695	149	5738	1.55148	0.9684143	0.105467	21.319
KEGG_PATHWAY	mmu05410:Hypertrophic cardiomyopathy (HCM)	18	0.81	0.0215	CACNA2D1, IL6, ACT1C, CACNG8, PRKAG2, LMNA, TGFB3, CACNB3, ITGA4, ITGB3, TPM2, TPM1, TGFB1, TPM3, TGFB2, ITGA9, ITGA5, ITGAV	695	84	5738	1.76917	0.9785393	0.113122	23.401
KEGG_PATHWAY	mmu05210:Colorectal cancer	18	0.81	0.0266	TRP53, TCF7, PIK3CD, TGFB3, LEF1, FZD3, BIRC5, TGFB1, RALGDS, TGFB2, FOS, RAC2, PDGFRA, PIK3R5, MYC, AKT3, AKT2, PIK3R2	695	86	5738	1.72802	0.9915369	0.134638	28.191
KEGG_PATHWAY	mmu04012:ErbB signaling pathway	18	0.81	0.0295	MAP2K4, PIK3CD, RPS6KB2, RPS6KB1, SRC, HRAS1, PRKCB, NRAS, EIF4EBP1, CDKN1A, EREG, PIK3R5, SHC1, MYC, CAMK2A, AKT3, AKT2, PIK3R2	695	87	5738	1.70816	0.9949969	0.144282	30.763
KEGG_PATHWAY	mmu04621:NOD-like receptor signaling pathway	14	0.63	0.0317	IL6, CCL2, CCL8, MAPK11, BIRC3, CCL5, MAP3K7, CCL12, MAPK13, CASP8, PSTPIP1, PYCARD, RIPK2, CASP1	695	62	5738	1.86428	0.9966728	0.150424	32.695
KEGG_PATHWAY	mmu05220:Chronic myeloid leukemia	16	0.72	0.0363	TRP53, PIK3CD, TGFB3, TGFB1, TGFB2, HRAS1, NRAS, CDKN1A, GAB2, PIK3R5, SHC1, RUNX1, MYC, AKT3, AKT2, PIK3R2	695	76	5738	1.73813	0.9985696	0.166347	36.525
KEGG_PATHWAY	mmu04640:Hematopoietic cell lineage	17	0.77	0.042	IL1R2, IL6, IL1R1, CSF1, IL4RA, ITGB3, ITGA4, CD1D1, FCGR1, KITL, IL11, CD44, GP1BB, ITGA5, CSF2RA, IL3RA, CD14	695	84	5738	1.67088	0.9994966	0.185553	40.962
KEGG_PATHWAY	mmu05414:Dilated cardiomyopathy	18	0.81	0.0475	ADCY3, CACNA2D1, ACT1C, ADCY7, CACNG8, LMNA, TGFB3, CACNB3, ITGB3, ITGA4, TPM2, TPM1, TGFB1, TGFB2, TPM3, ITGA9, ITGA5, ITGAV	695	92	5738	1.61533	0.9998183	0.202815	44.994
KEGG_PATHWAY	mmu04540:Gap junction	17	0.77	0.0507	ADCY3, CDK1, ADCY7, PRKG2, SRC, PRKCB, HRAS1, NRAS, CSNK1D, TUBB5, PDGFRA, TUBB6, GUCY1A3, GUCY1B3, HTR2B, PLCB1, TUBB3	695	86	5738	1.63202	0.9998992	0.210189	47.197
KEGG_PATHWAY	mmu05219:Bladder cancer	10	0.45	0.06	TRP53, NRAS, CDKN1A, MMP9, RASSF1, THBS1, DAPK3, MYC, MMP2, HRAS1	695	42	5738	1.96574	0.9999823	0.23935	53.206
KEGG_PATHWAY	mmu04142:Lysosome	21	0.95	0.0778	AP1M1, NAGLU, GM2A, GUSB, AP3S2, AP3S1, CTSS, SLC11A2, SLC11A1, CTSK, CD68, LAPTM5, AP1S2, GLA, CTSE, ATP6V0A1, CTSC, SCARB2, MAN2B1, GBA, IDUA	695	119	5738	1.45696	0.9999994	0.294998	63.011
KEGG_PATHWAY	mmu05214:Glioma	13	0.59	0.0793	TRP53, PIK3CD, PRKCB, HRAS1, NRAS, CDKN1A, PDGFRA, PIK3R5, SHC1, CAMK2A, AKT3, PIK3R2, AKT2	695	64	5738	1.67702	0.9999996	0.294001	63.748
KEGG_PATHWAY	mmu05218:Melanoma	14	0.63	0.0812	TRP53, FGF7, PIK3CD, FGF11, HGF, FGF12, HRAS1, NRAS, CDKN1A, PDGFRA, PIK3R5, AKT3, PIK3R2, AKT2	695	71	5738	1.62797	0.9999997	0.294432	64.678
KEGG_PATHWAY	mmu05222:Small cell lung cancer	16	0.72	0.0835	TRP53, CKS1B, PIK3CD, SKP2, BIRC3, CDK2, CCNE2, CCNE1, ITGAV, PIK3R5, TRAF5, MYC, AKT3, AKT2, PIK3R2, FN1	695	85	5738	1.55409	0.9999998	0.295712	65.713
KEGG_PATHWAY	mmu05212:Pancreatic cancer	14	0.63	0.0887	TRP53, PIK3CD, TGFB3, RALGDS, STAT3, TGFB1, TGFB2, RAD51, RAC2, RALA, PIK3R5, AKT3, AKT2, PIK3R2	695	72	5738	1.60536	0.9999999	0.306153	68.062
KEGG_PATHWAY	mmu05213:Endometrial cancer	11	0.5	0.0904	TRP53, NRAS, TCF7, PIK3CD, LEF1, PIK3R5, MYC, AKT3, AKT2, PIK3R2, HRAS1	695	52	5738	1.74649	0.9999999	0.305617	68.785
KEGG_PATHWAY	mmu04650:Natural killer cell mediated cytotoxicity	21	0.95	0.095	ITGB2, RAET1B, RAET1A, RAET1C, RAET1D, RAET1E, RAC2, PPP3CB, PPP3CC, FCER1G, NFATC4, SHC1, PIK3R5, NFATC2, NFATC1, TYROBP, PIK3R2, PIK3CD, FCGR4, FCGR3, PRKCB, HRAS1, NRAS, IFNAR2, SH3BP2	695	122	5738	1.42113	1	0.313359	70.658

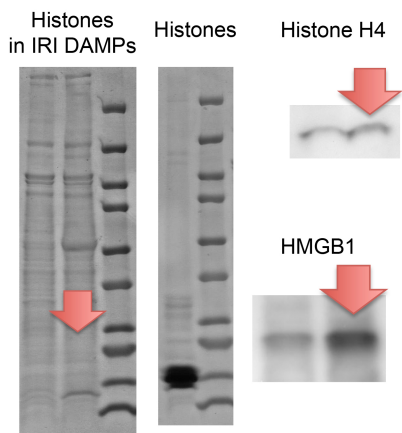
Supplemental Table 3**List of Taqman Gene Expression Assays used for transcript quantification**

Gene	Vendor	Format	Assay ID
<i>Acta2</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00725412_s1
<i>Ccl2</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00441242_m1
<i>Ccl3</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00441259_g1
<i>Cd80</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00711660_m1
<i>Col1a1</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00801666_g1
<i>Cxcl1</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm04207460_m1
<i>Cxcl10</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00445235_m1
<i>Cxcl2</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00436450_m1
<i>Gapdh</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm99999915_g1
<i>Icam1</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00516023_m1
<i>Il18</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00434225_m1
<i>Il1r1</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00434237_m1
<i>Il1β</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00434228_m1
<i>Il6</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00446190_m1
<i>Irak4</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00459443_m1
<i>Myd88</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00440338_m1
<i>Tlr2</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm01213946_g1
<i>Tlr4</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00445273_m1
<i>Tnfa</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm00443258_m1
<i>Vcam1</i>	Life Technologies	TaqMan® Gene Expression Assays	Mm01320970_m1
<i>ACTA2</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs00426835_g1
<i>CCL2</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs00234140_m1
<i>CCL3</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs04194942_s1
<i>COL1A1</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs00164004_m1
<i>CXCL1</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs00236937_m1
<i>CXCL10</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs01124251_g1
<i>CXCL2</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs00601975_m1
<i>GAPDH</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs02758991_g1
<i>ICAM1</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs00164932_m1
<i>IL1B</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs01555410_m1
<i>IL1R1</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs00991010_m1
<i>IL6</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs00985639_m1
<i>MYD88</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs01573837_g1
<i>TLR4</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs00152939_m1
<i>TNFA</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs01113624_g1
<i>VCAM1</i>	Life Technologies	TaqMan® Gene Expression Assays	Hs01003372_m1

Supplemental Table 4
List of siRNAs

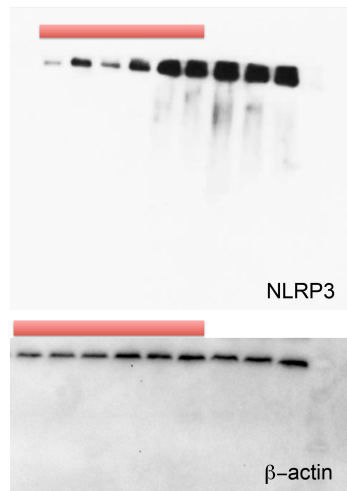
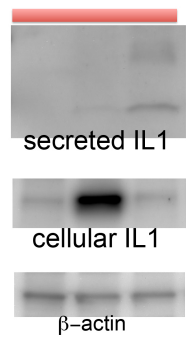
Gene	Vendor	Catalog No.	siRNA ID
<i>Il1r1</i>	Thermo Fisher	AM16708	158285
<i>Irak4</i>	Thermo Fisher	AM16708	152514
<i>Myd88</i>	Thermo Fisher	4390771	s201719
<i>Tlr2</i>	Thermo Fisher	AM16708	187990
<i>Tlr4</i>	Thermo Fisher	188776	AM16708
<i>IL1R1</i>	Thermo Fisher	AM16708	106303
<i>IRAK4</i>	Thermo Fisher	AM16708	134831
<i>MYD88</i>	Thermo Fisher	4390824	s9137

Full unedited gels for Figure 1 H

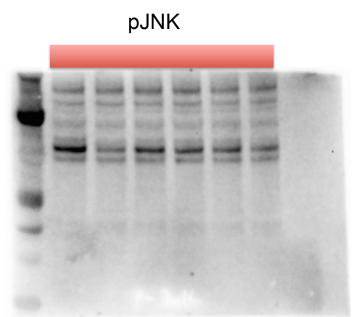
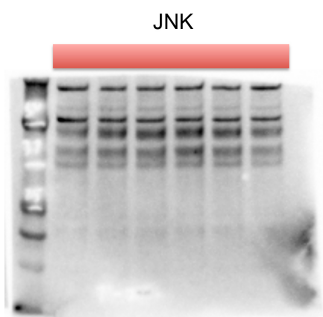
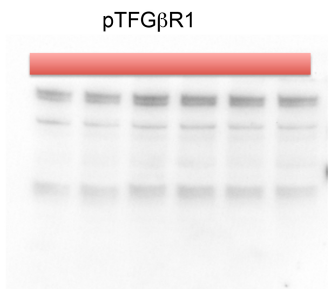
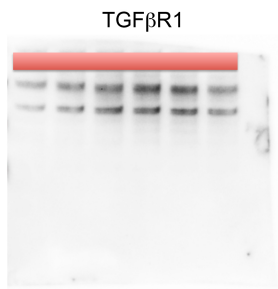
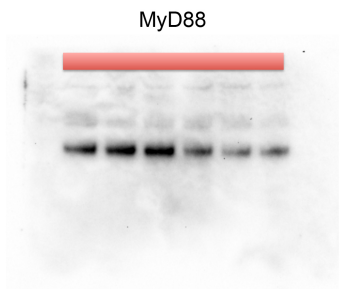


Full unedited gels for Figure 2C

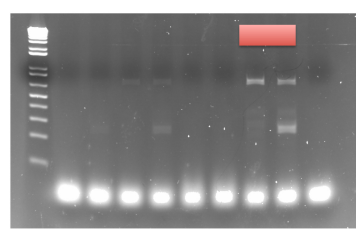
Available gels for Figure 2B



Full unedited gels for Figure S5 D



Full unedited gel for figure S6 B



Available gels for figure S6F

