Supplementary Data

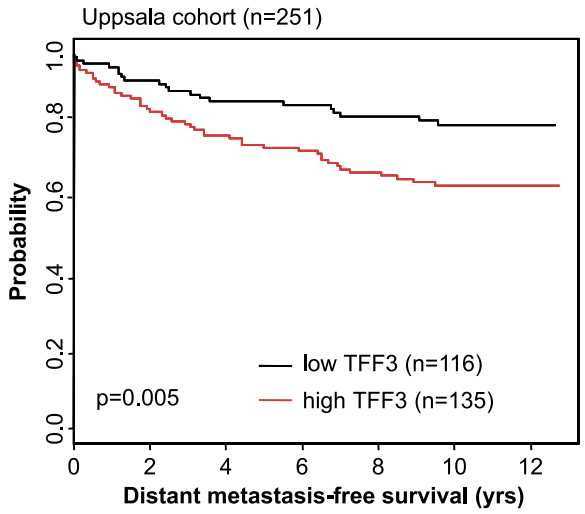


Figure W1. *TFF3* mRNA expression is correlated with decreased DMFS in breast cancer patients. 251 breast cancer patients of the Uppsala cohort were split into two groups: low *TFF3* expression (below mean) and high *TFF3* expression (above mean). The DMFS of these two groups was compared by Kaplan-Meier (K-M) analysis as described in the Materials and Methods section.

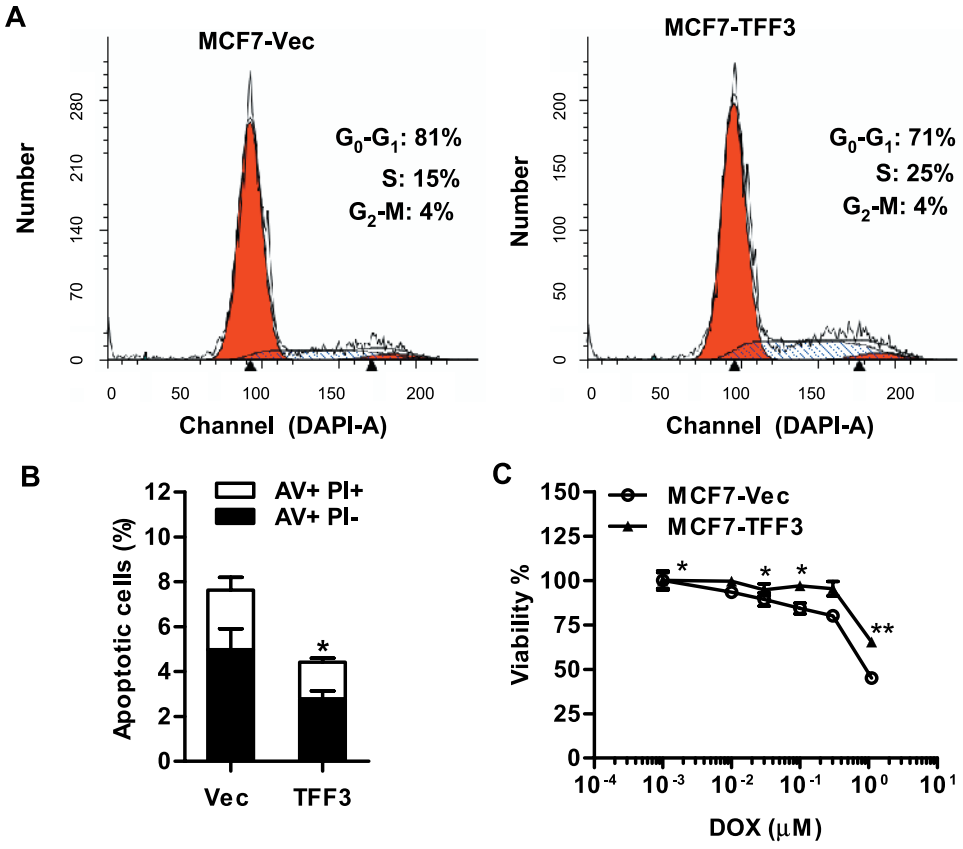


Figure W2. Forced expression of TFF3 increases cell cycle entry and reduces apoptosis of human mammary carcinoma cells. (A) Cell cycle analysis of MCF7-Vec and MCF7-TFF3 cells by DAPI staining after 24 hours of serum depletion. (B) Determination of early and late apoptosis of MCF7-Vec and MCF7-TFF3 cells by annexin V (AV) and propidium iodide (PI) double staining. Both early apoptosis (AV+ PI−) and later apoptosis (AV+ PI+) are presented as the percentage of total cells. (C) Cell viability of MCF7-Vec and MCF7-TFF3 cells after treatment with doxorubicin at various concentrations in 0.5% FBS for 3 days was determined by MTT assay. *$P < .05$, **$P < .01$.

Table W1. Sequences of Oligonucleotide Primers Used for Semiquantitative RT-PCR.

Genes	Abbreviation		Primer Sequence (5′-3′)	Amplicon Size (bp)
Trefoil factor 3	*TFF3*	Forward	GGCTGTGATTGCTGCCAG	125
		Reverse	GTGGAGCATGGGACCTTTAT	
Beta-actin	*β-ACTIN*	Forward	ATGATATCGCCGCGCTCG	580
		Reverse	CGCTCGGTGAGGATCTTCA	

Table W2. Sequences of Oligonucleotide Primers Used for qPCR.

Genes	Abbreviation		Primer Sequence (5′-3′)	Amplicon Size (bp)
v-akt murine thymoma viral oncogene homolog 1	*AKT1*	Forward	GCACAAACGAGGGGAGTACAT	113
		Reverse	CCTCACGTTGGTCCACATC	
v-raf murine sarcoma 3611 vial oncogene homolog 1	*ARAF1*	Forward	CTTGCTGTCCTCCAGCTCT	124
		Reverse	CCGGTTGTTGCACTCCTT	
Ataxia telangiectasia mutated	*ATM*	Forward	TGGATCCAGCTATTTGGTTTGA	82
		Reverse	CCAAGTATGTAACCAACAATAGAAGAAGTAG	
BCL2-antagonist of cell death	*BAD*	Forward	CCCAGAGTTTGAGCCGAGTG	249
		Reverse	CCCATCCCTTCGTCGTCCT	
BCL2-antagonist killer 1	*BAK1*	Forward	GAACAGGAGGCTGAAGGGGT	307
		Reverse	TCAGGCCATGCTGGTAGACG	
BCL2-associated X protein	*BAX*	Forward	GGGTGGTTGGGTGAGACTC	199
		Reverse	AGACACGTAAGGAAAACGCATTA	
B-cell CLL/lymphoma 2	*BCL2*	Forward	TCCGCATCAGGAAGGCTAGA	113
		Reverse	AGGACCAGGCCTCCAAGCT	
BCL2-like 1	*BCL2L1*	Forward	ATGGCAGCAGTAAAGCAAGC	149
		Reverse	CGGAAGAGTTCATTCACTACCTGT	
beta-Actin	*β-ACTIN*	Forward	TTCCTGGGCATGGAGTC	84
		Reverse	CAGGTCTTTGCGGATGTC	
Baculoviral IAP repeat-containing 5	*BIRC5*	Forward	TCCACTGCCCCACTGAGAAC	76
		Reverse	TGGCTCCCAGCCTTCCA	
Breast cancer 1, early onset	*BRCA1*	Forward	CATGCTGAAACTTCTCAACCAGAA	81
		Reverse	TGTAGGCTCCTTTTGGTTATATCATTC	
Caspase 7, apoptosis-related cysteine peptidase	*CASP7*	Forward	AGTGACAGGTATGGGCGTTCG	274
		Reverse	GCATCTATCCCCCCTAAAGTGG	
Cyclin A1	*CCNA1*	Forward	AAACTACTAAAGTCTAAGGGAAA	170
		Reverse	CTTCTACAATAAGTTTCTGAATG	
Cyclin Dl	*CCND1*	Forward	ACGAAGGTCTGCGCGTGTT	323
		Reverse	CCGCTGGCCATGAACTACCT	
Cyclin El	*CCNE1*	Forward	ATCAGCACTTTCTTGAGCAACA	122
		Reverse	TTGTGCCAAGTAAAAGGTCTCC	
Cell division cycle 25A	*CDC25A*	Forward	TAAGACCTGTATCTCGTGGCTG	131
		Reverse	CCCTGGTTCACTGCTATCTCT	
Cyclin-dependent kinase 1	*CDK1*	Forward	TCGAAAGCCAAGATAAGCAAC	137
		Reverse	CCGCAACAGGGAAGAACAGT	
Cyclin-dependent kinase 2	*CDK2*	Forward	GCTAGCAGACTTTGGACTAGCCAG	85
		Reverse	AGCTCGGTACCACAGGGTCA	
Cyclin-dependent kinase 4	*CDK4*	Forward	CTGGTGTTTGAGCATGTAGACC	102
		Reverse	AAACTGGCGCATCAGATCCTT	
Cyclin-dependent kinase inhibitor 1A (p21)	*CDKN1A*	Forward	CCTCATCCCGTGTTCTCCTTT	97
		Reverse	GTACCACCCAGCGGACAAGT	
Cyclin-dependent kinase inhibitor 1B (p27)	*CDKN1B*	Forward	CTGCAACCGACGATTCTTCTACT	101
		Reverse	GGGC GTC TGCTCCACAGA	
Cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	*CDKN2A*	Forward	CAACGCACCGAATAGTTACGG	96
		Reverse	AACTTCGTCCTCCAGAGTCGC	
Cadherin type 1	*CDH1*	Forward	ACACCCGGGACAACGTTTA	81
		Reverse	TGTGCAGCTGGCTCAAGTC	
Cadherin associated protein, alpha 1	*CTNNA1*	Forward	CCATGCAGGCAACATAAACTTC	81
		Reverse	GGCTCCAACAGTCTCTCAACT	
Cadherin associated protein, beta 1	*CTNNB1*	Forward	C CCACTGGCCTCTGATAAAGG	80
		Reverse	ACGCAAAGGTGCATGATTTG	
Cadherin associated protein, gamma	*CTNNG*	Forward	AACAAGAACAACCCCAAGTT	134
		Reverse	TAGTTACGCATGATCTGCAC	
E2F transcription factor 1	*E2F1*	Forward	AGATGGTTATGGTGATCAAAGCC	72
		Reverse	ATCTGAAAGTTCTCCGAAGAGTCC	
v-ets erythroblastosis virus E26 oncogene homolog 2	*ETS2*	Forward	CCCCTGTGGCTAACAGTTACA	222
		Reverse	AGGTAGCTTTTAAGGCTTGACTC	
Fibronectin 1	*FN1*	Forward	CCCATCAGCAGGAACACCTT	84
		Reverse	GGCTCACTGCAAAGACTTTGAA	
v-fos FBJ murine osteosarcoma viral oncogene homolog	*FOS*	Forward	TGCCTCTCCTCAATGACCCTGA	162
		Reverse	TGCCTCTCCTCAATGACCCTGA	
Glyceraldehyde-3-phosphate dehydrogenase	*GAPDH*	Forward	TGCACCACCAACTGCTTAGC	84
		Reverse	GGC ATGGACTGTGGTCATGAG	

Table W2. (*continued*)

Genes	Abbreviation		Primer Sequence (5′-3′)	Amplicon Size (bp)
Hypoxanthine phosphoribosyltransferase	*HPRT*	Forward	TGACACTGGCAAAACAATGCA	94
		Reverse	GGTCCTTTTCACCAGCAAGCT	
HIV-1 Tat interactive protein 2, 30 kDa	*HTATIP2*	Forward	CGGAGGGATTTGTTCGTGTTG	104
		Reverse	AGCTCCTTTAGAGGATAGCAAGT	
MET proto-oncogene hepatocyte growth factor receptor)	*MET*	Forward	TGGTGCAGAGGAGCAATGG	111
		Reverse	CATTCTGGATGGGTGTTTCCG	
Matrix metallopeptidase 1	*MMP1*	Forward	AGCTAGCTCAGGATGACATTGATG	74
		Reverse	GCCGATGGGCTGGACAG	
Matrix metallopeptidase 2	*MMP2*	Forward	CAAAAACAAGAAGACATACATCTT	232
		Reverse	GCTTCCAAACTTCACGCTC	
Matrix metallopeptidase 9	*MMP9*	Forward	TGGGGGGCAACTCGGC	224
		Reverse	GGAATGATCTAAGCCCAG	
Metastasis associated 1	*MTA1*	Forward	GCTGTTACACCACACAGTCTT	166
		Reverse	GGACTCATGTTACTGCGGTTT	
Metastasis associated 2	*MTA2*	Forward	CCGACGGCCTTATGCTCCT	145
		Reverse	CTGGGCCACCAGATCTTTGAC	
v-myc myelocytomatosis viral oncogene homolog (avian)	*MYC*	Forward	TGCTGCCAAGAGGGTCAAGT	118
		Reverse	GTGTGTTCGCCTCTTGACATTC	
Nuclear factor of kappa light polypeptide gene enhancer in B cells 1 (p105)	*NFκB1*	Forward	TGCCAACAGATGGCCCATAC	123
		Reverse	TGTTCTTTTCACTAGAGGCACCA	
Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	*NFκBIA*	Forward	CTCCGAGACTTTCGAGGAAATAC	135
		Reverse	GCCATTGTAGTTGGTAGCCTTCA	
Nonmetastatic cells 1 protein (NM23A)	*NME1*	Forward	GCTGCAGCCGGAGTTCAAAC	289
		Reverse	GCAATGAAGGTACGCTCACAGT	
Occludin	*OCLN*	Forward	TGCCGCGTTGGTGATCTTT	100
		Reverse	GCCCAGGATAGCACTCACTATT	
Plasminogen activator urokinase	*PLAU*	Forward	CACGCAAGGGGAGATGAA	341
		Reverse	ACAGCATTTTGGTGGTGACTT	
Plasminogen activator urokinase receptor	*PLA UR*	Forward	AATGGCCGCCAGTGTTACAG	227
		Reverse	CAGGAGACATCAATGTGGTTC	
v-raf-1 murine leukemia viral oncogene homolog 1	*RAF*	Forward	TTTCCTGGATCATGTTCCCCT	153
		Reverse	ACTTTGGTGCTACAGTGCTCA	
Retinoblastoma 1	*RB1*	Forward	GAACATCGAATCATGGAATCCCT	116
		Reverse	AGAGGACAAGCAGATTCAAGGTGAT	
SI00 calcium binding protein A4	*S100A4*	Forward	GATGAGCAACTTGGACAGCAA	123
		Reverse	CTGGGCTGCTTATCTGGGAAG	
Serpin peptidase inhibitor, clade B (ovalbumin), member 5	*SERPINB5*	Forward	CTACTTTGTTGGCAAGTGGATGAA	90
		Reverse	ACTGGTTTGGTGTCTGTCTTGTTG	
Serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1)	*SERPINE1*	Forward	CACAAATCAGACGGCAGCACT	85
		Reverse	CATCGGGCGTGGTGAACTC	
Snail homolog 1	*SNAIL*	Forward	AATCGGAAGCCTAACTACAGCG	147
		Reverse	GTCCCAGATGAGCATTGGCA	
Synuclein, gamma (breast cancer–specific protein 1)	*SNCG*	Forward	TGAGCAGCGTCAACACTGTG	64
		Reverse	GAGGTGACCGCGATGTTCTC	
Trefoil factor 1	*TFF1*	Forward	CATCGACGTCCCTCCAGAAGAG	105
		Reverse	CTCTGGGACTAATCACCGTGCTG	
Trefoil factor 3	*TFF3*	Forward	CTTGCTGTCCTCCAGCTCT	124
		Reverse	CCGGTTGTTGCACTCCTT	
Tumor necrosis factor receptor superfamily, member 1A	*TNFRSF1A*	Forward	TGCCTACCCCAGATTGAGAA	169
		Reverse	ATTTCCCACAAACAATGGAGTAG	
Tumor necrosis factor receptor superfamily member 10B	*TNFRSF10B*	Forward	AAGACCCTTGTGCTCGTTGT	144
		Reverse	AGGTGGAC ACAATCCCTCTG	
Tumor necrosis factor receptor superfamily member 25	*TNFRSF25*	Forward	ACTGCCAACCATGCCTAGACTG	155
		Reverse	GAGC CTCCATCCCAGCTTC	
Tumor protein p53 (Li-Fraumeni yndrome)	*TP53*	Forward	TGCAGCTGTGGGTTGATTCC	396
		Reverse	AAACACGCACCTCAAAGCTGTTC	
Vascular endothelial growth factor-A	*VEGF-A*	Forward	TACCTCCACCATGCCAAG	148
		Reverse	GGTACTCCTGGAAGATGTC	
Vimentin	*VIM*	Forward	CCTTGAACGCAAAGTGGAATC	106
		Reverse	GACATGCTGTTCCTGAATCTGAG	

Table W3. qPCR Analysis of Modulation of Gene Expression by Forced Expression of TFF3 in MCF-7 Cells.

Gene Function	Gene	Ratio (TFF3/Vec)*	*P*
Cell cycle control and DNA damage repair	*BRCA1*	0.93	7.30*e* – 01
	CDK1	2.41	3.90*e* – 04
	CDC25A	0.79	2.90*e* – 01
	CDC25C	1.13	4.00*e* – 01
	CDK2	0.64	2.20*e* – 02
	CDK4	0.87	5.00*e* – 03
	CDKN1A	0.46	1.90*e* – 04
	CDKN1B	1.01	7.80*e* – 01
	CDKN2A	1.02	8.10*e* – 01
	CCNA1	17.07	1.20*e* – 04
	CCNB1	1.01	5.30*e* – 01
	CCND1	0.61	3.20*e* – 01
	CCNE1	0.74	1.50*e* – 01
	E2F1	0.85	6.00*e* – 02
	RB1	0.94	6.60*e* – 01
	TP53	0.91	1.13*e* – 01
Adhesion and invasion	*CTNNA1*	0.96	8.60*e* – 01
	CTNNB1	0.99	9.60*e* – 01
	CDH1	0.74	3.00*e* – 02
	CTNNG	0.39	5.00*e* – 02
	FN1	2.43	1.00*e* – 02
	C-MET	1.36	1.40*e* – 01
	MMP1	1.28	4.80*e* – 01
	MMP2	0.98	6.20*e* – 01
	MMP9	1.08	8.40*e* – 01
	MTA1	0.93	3.00*e* – 01
	MTA2	0.98	8.60*e* – 01
	NME1	0.39	1.10*e* – 06
	OCLU	0.80	5.00*e* – 01
	PLAU	1.42	8.80*e* – 01
	PLAUR	0.59	4.00*e* – 02
	SERPINB5	1.25	3.30*e* – 01
	SERPINE1	0.78	5.60*e* – 01
	VEGF	1.35	1.80*e* – 01
	VIMENTIN	2.51	1.80*e* – 04
	SLUG	0.72	1.60*e* – 01
	SNAIL	1.25	1.10*e* – 01
	SNCG	0.27	1.10*e* – 03
Apoptosis	*ATM*	1.08	5.69*e* – 01
	ARAF	1.21	7.89*e* – 02
	BAD	0.84	4.35*e* – 01
	BAK1	1.01	7.70*e* – 01
	BAX	0.05	4.40*e* – 04
	BCL2	4.52	1.10*e* – 03
	BCL2L1	0.80	1.22*e* – 01
	CASP7	0.41	3.00*e* – 04
	MCL1	1.10	9.00*e* – 01
	S100A4	1.03	7.50*e* – 01
	BIRC5	1.26	1.40*e* – 01
	RAF	0.92	3.00*e* – 01
	HTATIP2	0.44	1.20*e* – 05
	TNFRSF10B	1.14	1.80*e* – 01
	TNFRSF1A	0.81	4.10*e* – 01
	TNFRSF25	1.89	4.00*e* – 03
Transcription factors	*ELF5*	0.80	6.00*e* – 01
	ETS2	1.12	6.40*e* – 01
	FOS	0.49	1.60*e* – 02
	NFκB1	1.19	2.70*e* – 01
	NFκBIA	2.94	1.59*e* – 02

*Average of three experiments represents each gene fold changes ($P < .05$). A positive value indicates increased gene expression and a negative value indicates decreased gene expression in MCF7-TFF3 cells relative to MCF7-Vec cells.

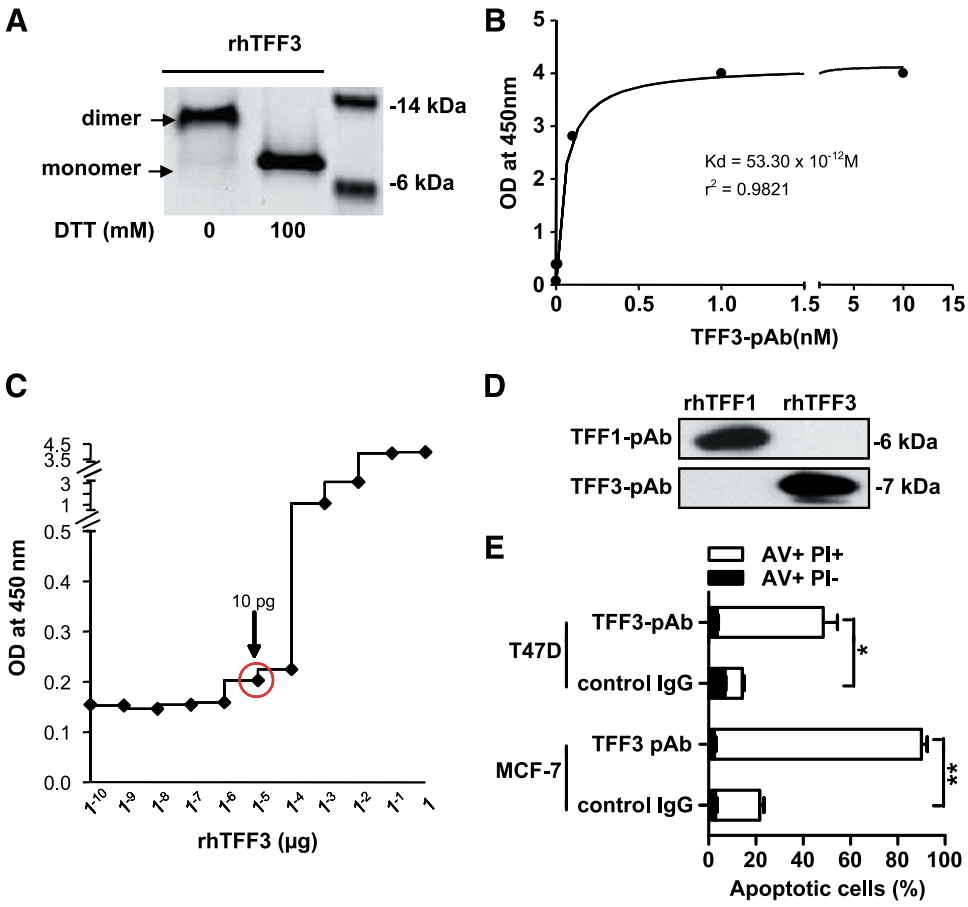


Figure W3. Production of rabbit polyclonal antibody against TFF3. (A) SDS-PAGE demonstrating formation of the monomeric and dimeric forms of rhTFF3 protein under nonreducing and reducing conditions, respectively. (B) Affinity binding of TFF3-pAb to rhTFF3 in an ELISA. A 96-well NUNC plate coated with 100 ng of rhTFF3 was incubated with various concentrations of rabbit TFF3-pAb. Bound antibodies were detected by incubation with goat antirabbit IgG conjugated with horseradish peroxidase and colorimetrically measured at 450 nm. (C) The detection limit of TFF3-pAb to rhTFF3 in an ELISA. A 96-well NUNC plate coated with various concentrations of rhTFF3 was incubated with 1 μg/ml TFF3-pAb. Bound antibodies were detected by incubation with goat antirabbit IgG conjugated with horseradish peroxidase and colorimetrically measured at 450 nm. (D) SDS-PAGE Western blot analysis of specificity of TFF3-pAb. Protein samples of purified rhTFF1 and rhTFF3 were subjected to SDS-PAGE. The proteins were transferred to a polyvinylidene fluoride membrane and probed by either rabbit TFF1-pAb (top panel) or rabbit TFF3-pAb (bottom panel). (E) MCF-7 and T47D cells were treated with TFF3-pAb at the concentration of 200 μg/ml in 0.5% FBS for 24 hours, and apoptosis was determined by annexin V and PI double staining as described in Materials and Methods.

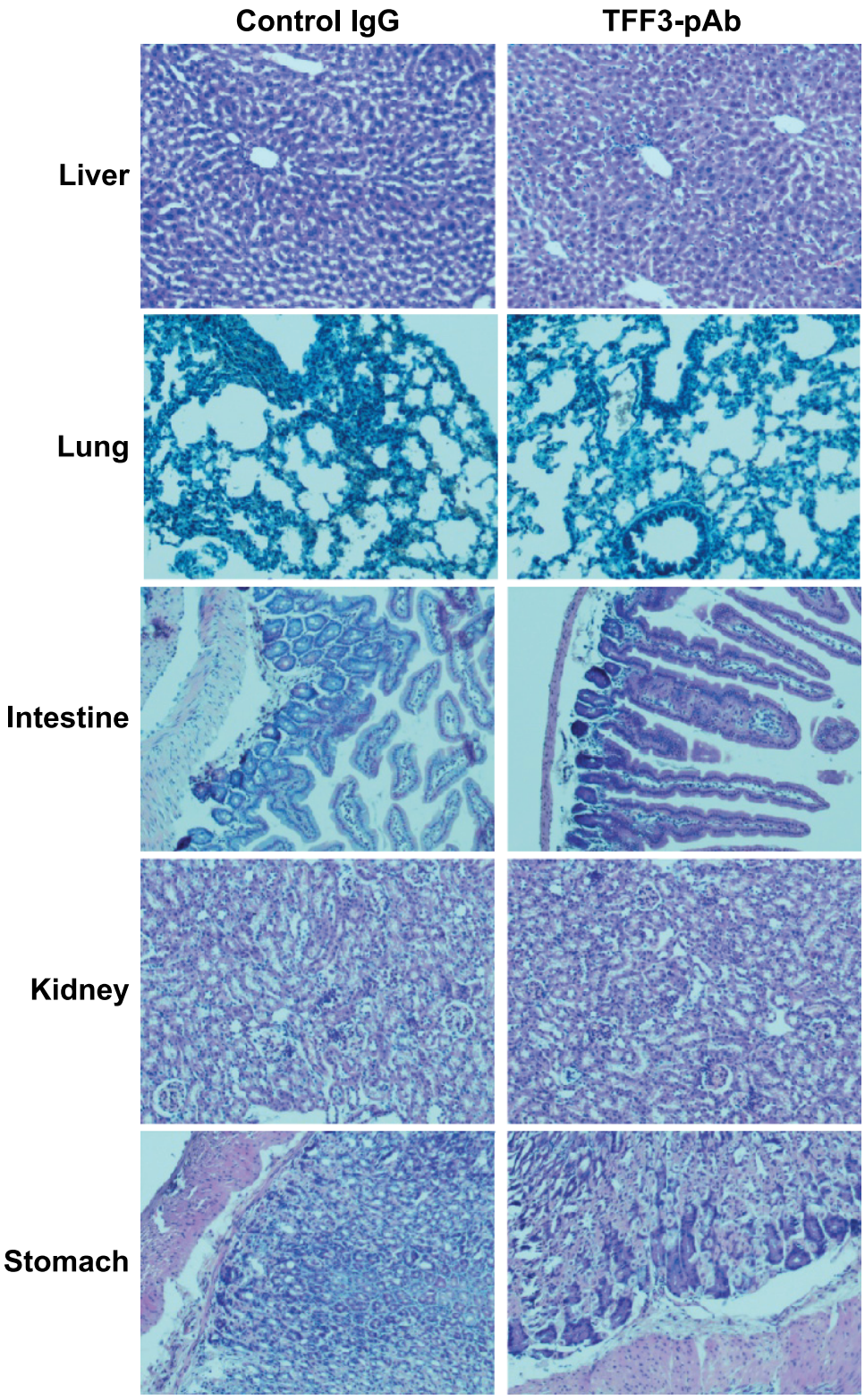
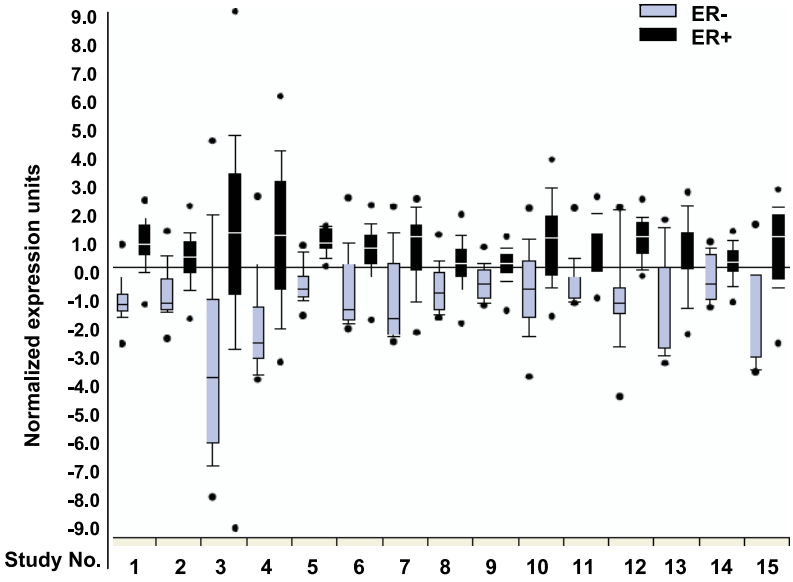


Figure W4. Effects of TFF3 polyclonal antibody treatment on morphologic aspects of vital organs of mice. TFF3-pAb was dosed 16 days after MCF-7 cell implantation and thereafter daily for 2 weeks. Histologic analyses with hematoxylin and eosin staining failed to identify any histologic alterations in the vital organs including liver, lung, intestine, kidney, and stomach between TFF3-pAb–treated mice and control IgG–treated mice.

Meta-analysis of Breast Cancer Microarray Data Sets

Data were collected from publicly available breast cancer microarray data sets in the cancer microarray database Oncomine (www.oncomine.org). *TFF3* gene expression was log-transformed, median-centered per array, and SD normalized to one per array. A meta-analysis approach was used to determine whether higher expression levels of the gene TFF3 was associated with ER+ or ER– status in breast cancer patients. Using *t* values and sample sizes from each study, we calculated effect sizes by the standardized mean difference method. The within-study variance for the effect size was calculated as the inverse of the study sample size. The pooled effect size was estimated in an intercept-only model with the study identifiers as random effects; this model was weighted by the between-study variance and the estimated within-study variances that were held constant. The meta-analysis was carried out using the MIXED procedure in SAS version 9.2 (SAS Institute, Inc, Cary, NC).



Analysis	Patient Number		P-value	Reference
	ER-	ER+		
1	42	57	4.30E-24	[1]
2	77	209	5.30E-20	[2]
3	69	226	1.40E-16	[3]
4	33	65	1.00E-12	[4]
5	24	15	8.00E-11	[5]
6	43	75	1.70E-10	[6]
7	51	82	1.80E-10	[7]
8	34	211	7.80E-08	[8]
9	34	213	1.60E-07	[9]
10	30	28	2.00E-06	[10]
11	28	27	5.50E-06	[11]
12	24	25	9.80E-06	[12]
13	18	56	3.10E-05	[13]
14	34	85	2.40E-04	[14]
15	11	24	2.60E-04	[15]
Combined			<0.0001	

Figure W5. *TFF3* expression is correlated with ER-positive status in human mammary carcinoma. Meta-analysis of *TFF3* gene expression profiles of human mammary carcinoma obtained from the Oncomine database showing a positive association of *TFF3* mRNA expression with ER-positive status in mammary carcinoma.

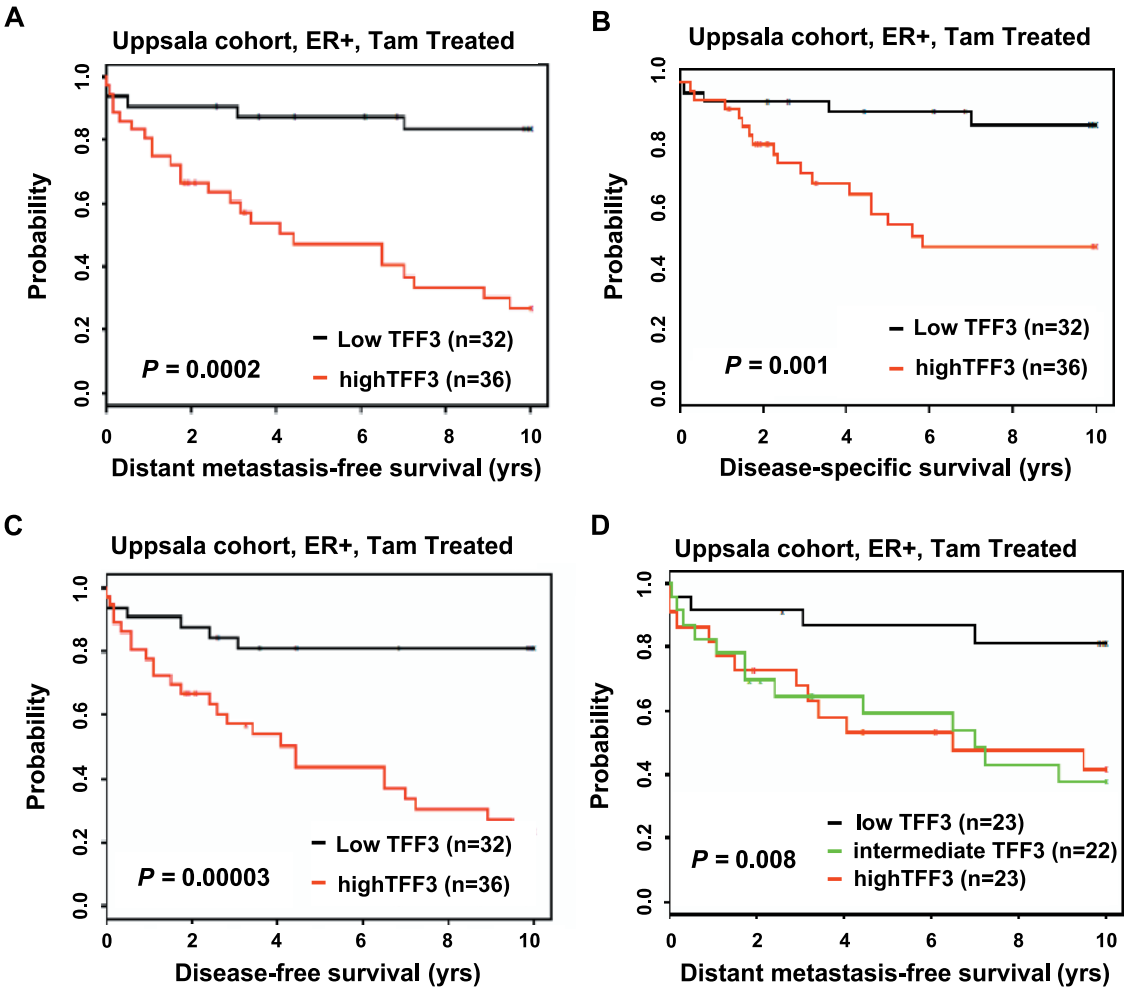


Figure W6. *TFF3* mRNA expression is correlated with decreased survival in patients with ER-positive breast cancer treated with tamoxifen. Kaplan-Meier analysis of the correlation of *TFF3* mRNA expression to DMFS (A and D), disease-specific survival (B) and disease-free survival (C) in tamoxifen-treated ER-positive breast cancer patients.

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