

**Table S1: Correlation of gene expression measured by RNA sequencing and qPCR.**

RNA Seq /qPCR			
Gene	Cell line	Pearson	p adjusted
<i>HBEGF</i>	MKN1	0.9008	0.0152
<i>HBEGF</i>	MKN7	0.9936	0.0509
<i>HBEGF</i>	Hs746T	-0.4851	0.8875
<i>HBEGF</i>	NCI-N87	0.9859	0.0699
<i>CD274</i>	NCI-N87	0.9969	0.0472
<i>CD274</i>	MKN7	0.9955	0.0509

**Table S2: Significantly enriched KEGG pathways in MKN1 cells after 4 h cetuximab treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
hsa05323	Rheumatoid arthritis	6/43	70/5844	0.00120571
hsa04657	IL-17 signaling pathway	6/43	79/5844	0.00121677
hsa04060	Cytokine-cytokine receptor interaction	8/43	186/5844	0.00198674
hsa04668	TNF signaling pathway	6/43	102/5844	0.00259938
hsa04010	MAPK signaling pathway	8/43	272/5844	0.01366521
hsa04062	Chemokine signaling pathway	6/43	145/5844	0.01366521
hsa05202	Transcriptional misregulation in cancer	6/43	168/5844	0.02194309
hsa05161	Hepatitis B	5/43	125/5844	0.0277262
hsa05132	Salmonella infection	4/43	75/5844	0.0277262
hsa05224	Breast cancer	5/43	139/5844	0.03890197
hsa04660	T cell receptor signaling pathway	4/43	89/5844	0.04230156
hsa05167	Kaposi's sarcoma-associated herpesvirus infection	5/43	155/5844	0.04767251
hsa04933	AGE-RAGE signaling pathway in diabetic complications	4/43	95/5844	0.04767251

**Table S3: Significantly enriched KEGG pathways in MKN1 cells after 24 h cetuximab treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
hsa05202	Transcriptional misregulation in cancer	10/72	168/5844	0.00617194

**Table S4: Significantly enriched Reactome pathways in MKN1 cells after 4 h cetuximab treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
380108	Chemokine receptors bind chemokines	5/39	31/5594	0.00039879
375276	Peptide ligand-binding receptors	6/39	119/5594	0.01591128

**Table S5: Significantly enriched KEGG pathways in MKN1 cells after 4 h EGF treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
hsa04657	IL-17 signaling pathway	11/103	79/5844	1.7557E-05
hsa04060	Cytokine-cytokine receptor interaction	15/103	186/5844	6.1425E-05
hsa04668	TNF signaling pathway	11/103	102/5844	8.2434E-05
hsa05323	Rheumatoid arthritis	8/103	70/5844	0.0011995
hsa05205	Proteoglycans in cancer	12/103	186/5844	0.00325511
hsa04621	NOD-like receptor signaling pathway	10/103	140/5844	0.00469904
hsa04390	Hippo signaling pathway	10/103	146/5844	0.00569143
hsa05132	Salmonella infection	7/103	75/5844	0.00707786
hsa05200	Pathways in cancer	19/103	469/5844	0.00883296
hsa05217	Basal cell carcinoma	6/103	58/5844	0.00883296
hsa05219	Bladder cancer	5/103	39/5844	0.00887918
hsa04012	ErbB signaling pathway	7/103	84/5844	0.00946041
hsa04062	Chemokine signaling pathway	9/103	145/5844	0.0130742
hsa04933	AGE-RAGE signaling pathway in diabetic complications	7/103	95/5844	0.01689209
hsa05161	Hepatitis B	8/103	125/5844	0.0179504
hsa05224	Breast cancer	8/103	139/5844	0.03198886
hsa05146	Amoebiasis	6/103	82/5844	0.03198886
hsa01522	Endocrine resistance	6/103	90/5844	0.04798049

**Table S6: Significantly enriched KEGG pathways in MKN1 cells after 24 h EGF treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
hsa04060	Cytokine-cytokine receptor interaction	31/389	186/5844	0.00038465
hsa05202	Transcriptional misregulation in cancer	26/389	168/5844	0.00537984
hsa04630	Jak-STAT signaling pathway	20/389	125/5844	0.01567177
hsa04974	Protein digestion and absorption	14/389	72/5844	0.01567177
hsa04510	Focal adhesion	26/389	190/5844	0.01718496
hsa04151	PI3K-Akt signaling pathway	35/389	296/5844	0.02233751
hsa04610	Complement and coagulation cascades	12/389	61/5844	0.02233751
hsa04512	ECM-receptor interaction	13/389	74/5844	0.03600776
hsa05205	Proteoglycans in cancer	24/389	186/5844	0.03787779

**Table S7: Significantly enriched Reactome pathways in MKN1 cells after 4 h EGF treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
380108	Chemokine receptors bind chemokines	7/98	31/5594	0.00027319
375276	Peptide ligand-binding receptors	9/98	119/5594	0.03119512
372790	Signaling by GPCR	19/98	453/5594	0.03119512
500792	GPCR ligand binding	13/98	253/5594	0.03754235

**Table S8: Significantly enriched Reactome pathways in MKN1 cells after 24 h EGF treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
373076	Class A/1 (Rhodopsin-like receptors)	39/379	202/5594	7.9336E-07
500792	GPCR ligand binding	44/379	253/5594	1.0274E-06
375276	Peptide ligand-binding receptors	26/379	119/5594	1.3179E-05
1474228	Degradation of the extracellular matrix	21/379	99/5594	0.00032029
1442490	Collagen degradation	15/379	57/5594	0.00046803
372790	Signaling by GPCR	56/379	453/5594	0.00048009
3000178	ECM proteoglycans	15/379	59/5594	0.00048009
2022090	Assembly of collagen fibrils and other multimeric structures	12/379	39/5594	0.00048009
388396	GPCR downstream signaling	48/379	387/5594	0.00157328
1474244	Extracellular matrix organization	32/379	227/5594	0.00322589
380108	Chemokine receptors bind chemokines	9/379	31/5594	0.00876351
446107	Type I hemidesmosome assembly	5/379	10/5594	0.01465555
879518	Transport of organic anions	5/379	11/5594	0.0230509
216083	Integrin cell surface interactions	14/379	76/5594	0.0230509
1474290	Collagen formation	13/379	69/5594	0.0271921
418594	G alpha (i) signalling events	18/379	116/5594	0.02980547
140875	Common Pathway of Fibrin Clot Formation	6/379	19/5594	0.04380188
2022870	Chondroitin sulfate biosynthesis	6/379	19/5594	0.04380188

**Table S9: Significantly enriched KEGG pathways in NCI-N87 cells after 4 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
hsa04668	TNF signaling pathway	11/147	102/5844	0.00964085
hsa05132	Salmonella infection	9/147	75/5844	0.01059343
hsa04060	Cytokine-cytokine receptor interaction	14/147	186/5844	0.01599995

**Table S10: Significantly enriched KEGG pathways in NCI-N87 cells after 24 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
hsa03030	DNA replication	32/1970	33/5844	4.4939E-12
hsa03008	Ribosome biogenesis in eukaryotes	51/1970	69/5844	1.2039E-09
hsa04110	Cell cycle	75/1970	118/5844	2.2175E-09
hsa00240	Pyrimidine metabolism	51/1970	89/5844	0.00022402
hsa03430	Mismatch repair	17/1970	20/5844	0.00022402
hsa03013	RNA transport	76/1970	150/5844	0.00054916
hsa03050	Proteasome	26/1970	40/5844	0.00215398
hsa03440	Homologous recombination	23/1970	35/5844	0.00402141
hsa00230	Purine metabolism	75/1970	157/5844	0.00524042
hsa03460	Fanconi anemia pathway	28/1970	47/5844	0.00659236
hsa03410	Base excision repair	20/1970	30/5844	0.00659236
hsa03020	RNA polymerase	17/1970	26/5844	0.02392305
hsa03040	Spliceosome	57/1970	120/5844	0.02583331

**Table S11: Significantly enriched Reactome pathways in NCI-N87 cells after 24 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
1640170	Cell Cycle	262/1891	462/5594	4.5934E-23
69278	Cell Cycle, Mitotic	221/1891	380/5594	3.1704E-21
453279	Mitotic G1-G1/S phases	81/1891	114/5594	8.6401E-14
69242	S Phase	78/1891	110/5594	2.8328E-13
69306	DNA Replication	68/1891	92/5594	5.238E-13
69206	G1/S Transition	68/1891	94/5594	2.6703E-12
69239	Synthesis of DNA	64/1891	88/5594	9.1325E-12
2500257	Resolution of Sister Chromatid Cohesion	62/1891	85/5594	1.4512E-11
2555396	Mitotic Metaphase and Anaphase	94/1891	149/5594	1.4512E-11
68877	Mitotic Prometaphase	65/1891	91/5594	1.508E-11
2467813	Separation of Sister Chromatids	90/1891	141/5594	1.508E-11
5663220	RHO GTPases Activate Formins	67/1891	95/5594	1.5703E-11
68882	Mitotic Anaphase	93/1891	148/5594	1.9281E-11
68886	M Phase	123/1891	216/5594	7.1954E-11
69190	DNA strand elongation	29/1891	31/5594	2.6593E-10
69620	Cell Cycle Checkpoints	75/1891	116/5594	4.376E-10
69481	G2/M Checkpoints	39/1891	49/5594	3.0847E-09
68874	M/G1 Transition	51/1891	72/5594	6.2252E-09
69002	DNA Replication Pre-Initiation	51/1891	72/5594	6.2252E-09
68962	Activation of the pre-replicative complex	25/1891	28/5594	7.605E-08
180786	Extension of Telomeres	22/1891	24/5594	2.2875E-07
73886	Chromosome Maintenance	47/1891	69/5594	2.2875E-07
113510	E2F mediated regulation of DNA replication	24/1891	28/5594	8.3859E-07
176187	Activation of ATR in response to replication stress	28/1891	35/5594	1.018E-06
162909	Host Interactions of HIV factors	69/1891	118/5594	1.018E-06
174417	Telomere C-strand (Lagging Strand) Synthesis	20/1891	22/5594	1.4433E-06
69300	Removal of licensing factors from origins	42/1891	64/5594	5.8719E-06
69304	Regulation of DNA replication	42/1891	64/5594	5.8719E-06
195258	RHO GTPase Effectors	108/1891	213/5594	5.8719E-06
69186	Lagging Strand Synthesis	18/1891	20/5594	9.1619E-06
68867	Assembly of the pre-replicative complex	39/1891	59/5594	1.1432E-05
68949	Orc1 removal from chromatin	40/1891	62/5594	2.0015E-05
69052	Switching of origins to a post-replicative state	40/1891	62/5594	2.0015E-05
174411	Polymerase switching on the C-strand of the telomere	13/1891	13/5594	2.0098E-05
69091	Polymerase switching	13/1891	13/5594	2.0098E-05
69109	Leading Strand Synthesis	13/1891	13/5594	2.0098E-05
177243	Interactions of Rev with host cellular proteins	24/1891	32/5594	5.7049E-05
176974	Unwinding of DNA	11/1891	11/5594	0.00017
109977	Repair synthesis for gap-filling by DNA polymerase in TC-NER	13/1891	14/5594	0.00017
74967	Repair synthesis of patch ~27-30 bases long by DNA polymerase	13/1891	14/5594	0.00017
73894	DNA Repair	70/1891	134/5594	0.00017
165054	Rev-mediated nuclear export of HIV RNA	22/1891	30/5594	0.00024

<b>180746</b>	Nuclear import of Rev protein	22/1891	30/5594	0.00024
<b>72203</b>	Processing of Capped Intron-Containing Pre-mRNA	60/1891	112/5594	0.00024
<b>162906</b>	HIV Infection	97/1891	201/5594	0.00024
<b>194315</b>	Signaling by Rho GTPases	143/1891	317/5594	0.00024
<b>191859</b>	snRNP Assembly	17/1891	21/5594	0.00025
<b>194441</b>	Metabolism of non-coding RNA	17/1891	21/5594	0.00025
<b>109979</b>	Gap-filling DNA repair synthesis and ligation in TC-NER	14/1891	16/5594	0.00028
<b>74969</b>	Gap-filling DNA repair synthesis and ligation in GG-NER	14/1891	16/5594	0.00028
<b>69202</b>	Cyclin E associated events during G1/S transition	34/1891	55/5594	0.00035
<b>69166</b>	Removal of the Flap Intermediate	12/1891	13/5594	0.00036
<b>69205</b>	G1/S-Specific Transcription	12/1891	13/5594	0.00036
<b>68827</b>	CDT1 association with the CDC6:ORC:origin complex	33/1891	53/5594	0.00036
<b>390466</b>	Chaperonin-mediated protein folding	20/1891	27/5594	0.00039
<b>72163</b>	mRNA Splicing - Major Pathway	57/1891	108/5594	0.00056
<b>72172</b>	mRNA Splicing	57/1891	108/5594	0.00056
<b>69183</b>	Processive synthesis on the lagging strand	13/1891	15/5594	0.00062
<b>174143</b>	APC/C-mediated degradation of cell cycle proteins	42/1891	74/5594	0.00063
<b>453276</b>	Regulation of mitotic cell cycle	42/1891	74/5594	0.00063
<b>389957</b>	Prefoldin mediated transfer of substrate to CCT/TriC	19/1891	26/5594	0.00076
<b>389958</b>	Cooperation of Prefoldin and TriC/CCT in actin and tubulin folding	19/1891	26/5594	0.00076
<b>157579</b>	Telomere Maintenance	27/1891	42/5594	0.00078
<b>72165</b>	mRNA Splicing - Minor Pathway	25/1891	38/5594	0.00082
<b>5357801</b>	Programmed Cell Death	70/1891	141/5594	0.00093
<b>389960</b>	Formation of tubulin folding intermediates by CCT/TriC	15/1891	19/5594	0.00106
<b>210991</b>	Basigin interactions	17/1891	23/5594	0.00140
<b>379716</b>	Cytosolic tRNA aminoacylation	17/1891	23/5594	0.00140
<b>189200</b>	Hexose transport	25/1891	39/5594	0.00145
<b>70153</b>	Glucose transport	24/1891	37/5594	0.00149
<b>176033</b>	Interactions of Vpr with host cellular proteins	22/1891	33/5594	0.00156
<b>5389840</b>	Mitochondrial translation elongation	39/1891	70/5594	0.00172
<b>5651801</b>	PCNA-Dependent Long Patch Base Excision Repair	13/1891	16/5594	0.00181
<b>77588</b>	SLBP Dependent Processing of Replication-Dependent Histone Pre-mRNAs	10/1891	11/5594	0.00195
<b>15869</b>	Metabolism of nucleotides	41/1891	75/5594	0.00197
<b>176814</b>	Activation of APC/C and APC/C:Cdc20 mediated degradation of mitotic proteins	37/1891	66/5594	0.00203
<b>110373</b>	Resolution of AP sites via the multiple-nucleotide patch replacement pathway	14/1891	18/5594	0.00215
<b>5607761</b>	Dectin-1 mediated noncanonical NF-kB signaling	31/1891	53/5594	0.00234
<b>69656</b>	Cyclin A:Cdk2-associated events at S phase entry	31/1891	53/5594	0.00234
<b>109581</b>	Apoptosis	67/1891	138/5594	0.00252
<b>176408</b>	Regulation of APC/C activators between G1/S and early anaphase	38/1891	69/5594	0.00258
<b>168325</b>	Viral Messenger RNA Synthesis	18/1891	26/5594	0.00276
<b>170822</b>	Regulation of Glucokinase by Glucokinase Regulatory Protein	19/1891	28/5594	0.00276
<b>180910</b>	Vpr-mediated nuclear import of PICs	20/1891	30/5594	0.00276
<b>5358565</b>	Mismatch repair (MMR) directed by MSH2:MSH6 (MutSalpha)	11/1891	13/5594	0.00278
<b>69601</b>	Ubiquitin Mediated Degradation of Phosphorylated Cdc25A	28/1891	47/5594	0.00278

69610	p53-Independent DNA Damage Response	28/1891	47/5594	0.00278
69613	p53-Independent G1/S DNA damage checkpoint	28/1891	47/5594	0.00278
169911	Regulation of Apoptosis	27/1891	45/5594	0.00291
69229	Ubiquitin-dependent degradation of Cyclin D1	27/1891	45/5594	0.00291
75815	Ubiquitin-dependent degradation of Cyclin D	27/1891	45/5594	0.00291
176409	APC/C:Cdc20 mediated degradation of mitotic proteins	36/1891	65/5594	0.00291
179419	APC:Cdc20 mediated degradation of cell cycle proteins prior to satisfaction of the cell cycle checkpoint	35/1891	63/5594	0.00316
74159	Transcription	70/1891	147/5594	0.00324
69473	G2/M DNA damage checkpoint	12/1891	15/5594	0.00338
69615	G1/S DNA Damage Checkpoints	30/1891	52/5594	0.00340
111367	SLBP independent Processing of Histone Pre-mRNAs	9/1891	10/5594	0.00404
180585	Vif-mediated degradation of APOBEC3G	28/1891	48/5594	0.00408
1538133	G0 and Early G1	14/1891	19/5594	0.00432
2151201	Transcriptional activation of mitochondrial biogenesis	14/1891	19/5594	0.00432
3301854	Nuclear Pore Complex (NPC) Disassembly	20/1891	31/5594	0.00432
187577	SCF(Skp2)-mediated degradation of p27/p21	27/1891	46/5594	0.00432
450531	Regulation of mRNA stability by proteins that bind AU-rich elements	41/1891	78/5594	0.00437
983189	Kinesins	15/1891	21/5594	0.00446
211733	Regulation of activated PAK-2p34 by proteasome mediated degradation	26/1891	44/5594	0.00454
350562	Regulation of ornithine decarboxylase (ODC)	26/1891	44/5594	0.00454
69017	CDK-mediated phosphorylation and removal of Cdc6	26/1891	44/5594	0.00454
174184	Cdc20:Phospho-APC/C mediated degradation of Cyclin A	34/1891	62/5594	0.00458
5368287	Mitochondrial translation	40/1891	76/5594	0.00467
1236978	Cross-presentation of soluble exogenous antigens (endosomes)	24/1891	40/5594	0.00531
111447	Activation of BAD and translocation to mitochondria	10/1891	12/5594	0.00538
75035	Chk1/Chk2(Cds1) mediated inactivation of Cyclin B:Cdk1 complex	10/1891	12/5594	0.00538
174113	SCF-beta-TrCP mediated degradation of Emi1	28/1891	49/5594	0.00562
5419276	Mitochondrial translation termination	37/1891	70/5594	0.00644
5358508	Mismatch Repair	11/1891	14/5594	0.00670
391251	Protein folding	20/1891	32/5594	0.00688
73847	Purine metabolism	20/1891	32/5594	0.00688
69231	Cyclin D associated events in G1	18/1891	28/5594	0.00765
69236	G1 Phase	18/1891	28/5594	0.00765
419524	Fanconi Anemia pathway	16/1891	24/5594	0.00822
114452	Activation of BH3-only proteins	15/1891	22/5594	0.00829
174178	APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1	34/1891	64/5594	0.00867
180534	Vpu mediated degradation of CD4	26/1891	46/5594	0.00999
425374	Amino acid and oligopeptide SLC transporters	25/1891	44/5594	0.01107
202733	Cell surface interactions at the vascular wall	42/1891	84/5594	0.01162
174414	Processive synthesis on the C-strand of the telomere	9/1891	11/5594	0.01180
73817	Purine ribonucleoside monophosphate biosynthesis	9/1891	11/5594	0.01180
73884	Base Excision Repair	19/1891	31/5594	0.01180
425407	SLC-mediated transmembrane transport	99/1891	229/5594	0.01180

<b>352230</b>	Amino acid transport across the plasma membrane	18/1891	29/5594	0.01228
<b>450408</b>	AUF1 (hnRNP D0) destabilizes mRNA	27/1891	49/5594	0.01228
<b>69563</b>	p53-Dependent G1 DNA Damage Response	27/1891	49/5594	0.01228
<b>69580</b>	p53-Dependent G1/S DNA damage checkpoint	27/1891	49/5594	0.01228
<b>3108214</b>	SUMOylation of DNA damage response and repair proteins	36/1891	70/5594	0.01228
<b>3108232</b>	SUMO E3 ligases SUMOylate target proteins	36/1891	70/5594	0.01228
<b>5368286</b>	Mitochondrial translation initiation	36/1891	70/5594	0.01228
<b>1236974</b>	ER-Phagosome pathway	30/1891	56/5594	0.01256
<b>2990846</b>	SUMOylation	38/1891	75/5594	0.01279
<b>5358606</b>	Mismatch repair (MMR) directed by MSH2:MSH3 (MutSbeta)	10/1891	13/5594	0.01308
<b>110314</b>	Recognition of DNA damage by PCNA-containing replication complex	16/1891	25/5594	0.01325
<b>606279</b>	Deposition of new CENPA-containing nucleosomes at the centromere	22/1891	38/5594	0.01325
<b>774815</b>	Nucleosome assembly	22/1891	38/5594	0.01325
<b>69541</b>	Stabilization of p53	26/1891	47/5594	0.01325
<b>1169408</b>	ISG15 antiviral mechanism	32/1891	61/5594	0.01332
<b>1169410</b>	Antiviral mechanism by IFN-stimulated genes	32/1891	61/5594	0.01332
<b>73780</b>	RNA Polymerase III Chain Elongation	11/1891	15/5594	0.01365
<b>73980</b>	RNA Polymerase III Transcription Termination	11/1891	15/5594	0.01365
<b>3371453</b>	Regulation of HSF1-mediated heat shock response	28/1891	52/5594	0.01482
<b>109688</b>	Cleavage of Growing Transcript in the Termination Region	24/1891	43/5594	0.01568
<b>73856</b>	RNA Polymerase II Transcription Termination	24/1891	43/5594	0.01568
<b>76044</b>	Post-Elongation Processing of the Transcript	24/1891	43/5594	0.01568
<b>4641258</b>	degradation of DVL	27/1891	50/5594	0.01630
<b>109606</b>	Intrinsic Pathway for Apoptosis	19/1891	32/5594	0.01680
<b>2980766</b>	Nuclear Envelope Breakdown	23/1891	41/5594	0.01724
<b>1268020</b>	Mitochondrial protein import	18/1891	30/5594	0.01801
<b>73933</b>	Resolution of Abasic Sites (AP sites)	18/1891	30/5594	0.01801
<b>983168</b>	Antigen processing: Ubiquitination & Proteasome degradation	26/1891	48/5594	0.01801
<b>379724</b>	tRNA Aminoacylation	22/1891	39/5594	0.01884
<b>68875</b>	Mitotic Prophase	36/1891	72/5594	0.01941
<b>349425</b>	Autodegradation of the E3 ubiquitin ligase COP1	25/1891	46/5594	0.01970
<b>5610783</b>	Degradation of GLI2 by the proteasome	28/1891	53/5594	0.01970
<b>1236975</b>	Antigen processing-Cross presentation	33/1891	65/5594	0.02045
<b>70263</b>	Gluconeogenesis	16/1891	26/5594	0.02071
<b>113507</b>	E2F-enabled inhibition of pre-replication complex formation	8/1891	10/5594	0.02250
<b>983169</b>	Class I MHC mediated antigen processing & presentation	39/1891	80/5594	0.02280
<b>4641257</b>	degradation of AXIN	26/1891	49/5594	0.02451
<b>73937</b>	Transcription-coupled NER (TC-NER)	22/1891	40/5594	0.02713
<b>174154</b>	APC/C:Cdc20 mediated degradation of Securin	30/1891	59/5594	0.02884
<b>73857</b>	RNA Polymerase II Transcription	47/1891	101/5594	0.02942
<b>5610780</b>	Degradation of GLI1 by the proteasome	27/1891	52/5594	0.03002
<b>1592230</b>	Mitochondrial biogenesis	16/1891	27/5594	0.03340
<b>5362768</b>	Hh mutants that don't undergo autocatalytic processing are degraded by ERAD	25/1891	48/5594	0.03802
<b>5387390</b>	Hh mutants abrogate ligand secretion	25/1891	48/5594	0.03802

<b>112297</b>	Post-Elongation Processing of Intronless pre-mRNA	14/1891	23/5594	0.03964
<b>75067</b>	Processing of Capped Intronless Pre-mRNA	14/1891	23/5594	0.03964
<b>5610785</b>	GLI3 is processed to GLI3R by the proteasome	27/1891	53/5594	0.04038
<b>109970</b>	Global Genomic NER (GG-NER)	18/1891	32/5594	0.04118
<b>73890</b>	Double-Strand Break Repair	13/1891	21/5594	0.04259
<b>162587</b>	HIV Life Cycle	56/1891	126/5594	0.04295

**Table S12: Significantly enriched KEGG pathways in MKN1 cells after 4 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
<b>hsa04668</b>	TNF signaling pathway	10/66	102/5844	2.3777E-05
<b>hsa05323</b>	Rheumatoid arthritis	8/66	70/5844	7.028E-05
<b>hsa04657</b>	IL-17 signaling pathway	8/66	79/5844	0.00011952
<b>hsa04060</b>	Cytokine-cytokine receptor interaction	11/66	186/5844	0.00022227
<b>hsa04933</b>	AGE-RAGE signaling pathway in diabetic complications	8/66	95/5844	0.00028978
<b>hsa04010</b>	MAPK signaling pathway	11/66	272/5844	0.00427566
<b>hsa05132</b>	Salmonella infection	6/66	75/5844	0.00427566
<b>hsa05142</b>	Chagas disease (American trypanosomiasis)	6/66	81/5844	0.00519986
<b>hsa05144</b>	Malaria	4/66	35/5844	0.01002006
<b>hsa05206</b>	MicroRNAs in cancer	7/66	149/5844	0.02029889
<b>hsa05167</b>	Kaposi's sarcoma-associated herpesvirus infection	7/66	155/5844	0.02319695
<b>hsa05200</b>	Pathways in cancer	13/66	469/5844	0.02329389
<b>hsa04064</b>	NF-kappa B signaling pathway	5/66	82/5844	0.02329389
<b>hsa05146</b>	Amoebiasis	5/66	82/5844	0.02329389
<b>hsa05134</b>	Legionellosis	4/66	50/5844	0.02329389
<b>hsa05202</b>	Transcriptional misregulation in cancer	7/66	168/5844	0.024013
<b>hsa05161</b>	Hepatitis B	6/66	125/5844	0.024013
<b>hsa05166</b>	HTLV-I infection	8/66	231/5844	0.03368798
<b>hsa05140</b>	Leishmaniasis	4/66	59/5844	0.03368798
<b>hsa04621</b>	NOD-like receptor signaling pathway	6/66	140/5844	0.0343651
<b>hsa04610</b>	Complement and coagulation cascades	4/66	61/5844	0.0343651
<b>hsa04062</b>	Chemokine signaling pathway	6/66	145/5844	0.03858289
<b>hsa05133</b>	Pertussis	4/66	65/5844	0.03936097
<b>hsa04640</b>	Hematopoietic cell lineage	4/66	69/5844	0.04657383

**Table S13: Significantly enriched KEGG pathways in MKN1 cells after 24 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
<b>hsa04640</b>	Hematopoietic cell lineage	11/206	69/5844	0.00617019



**Table S14: Significantly enriched Reactome pathways in MKN1 cells after 4 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
380108	Chemokine receptors bind chemokines	5/60	31/5594	0.00376562
937061	TRIF-mediated TLR3/TLR4 signaling	6/60	76/5594	0.00709969
450282	MAPK targets/ Nuclear events mediated by MAP kinases	4/60	26/5594	0.00709969
166166	MyD88-independent TLR3/TLR4 cascade	6/60	77/5594	0.00709969
168164	Toll Like Receptor 3 (TLR3) Cascade	6/60	77/5594	0.00709969
166054	Activated TLR4 signalling	6/60	89/5594	0.01312667
166016	Toll Like Receptor 4 (TLR4) Cascade	6/60	92/5594	0.01346718
198753	ERK/MAPK targets	3/60	17/5594	0.0159905
168898	Toll-Like Receptors Cascades	6/60	105/5594	0.0159905
166058	MyD88:Mal cascade initiated on plasma membrane	5/60	71/5594	0.0159905
168179	Toll Like Receptor TLR1:TLR2 Cascade	5/60	71/5594	0.0159905
168188	Toll Like Receptor TLR6:TLR2 Cascade	5/60	71/5594	0.0159905
181438	Toll Like Receptor 2 (TLR2) Cascade	5/60	71/5594	0.0159905
198725	Nuclear Events (kinase and transcription factor activation)	3/60	20/5594	0.01917469
373076	Class A/1 (Rhodopsin-like receptors)	8/60	202/5594	0.01917469
500792	GPCR ligand binding	9/60	253/5594	0.01917469
375276	Peptide ligand-binding receptors	6/60	119/5594	0.02157578
450294	MAP kinase activation in TLR cascade	4/60	49/5594	0.02248863
168180	TRAF6 Mediated Induction of proinflammatory cytokines	4/60	56/5594	0.03492941
3000178	ECM proteoglycans	4/60	59/5594	0.04014859
975138	TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	4/60	64/5594	0.04380237
168142	Toll Like Receptor 10 (TLR10) Cascade	4/60	65/5594	0.04380237
168176	Toll Like Receptor 5 (TLR5) Cascade	4/60	65/5594	0.04380237
168181	Toll Like Receptor 7/8 (TLR7/8) Cascade	4/60	65/5594	0.04380237
975155	MyD88 dependent cascade initiated on endosome	4/60	65/5594	0.04380237
975871	MyD88 cascade initiated on plasma membrane	4/60	65/5594	0.04380237
168138	Toll Like Receptor 9 (TLR9) Cascade	4/60	67/5594	0.04699983
381042	PERK regulates gene expression	2/60	11/5594	0.04751258
1989781	PPARA activates gene expression	3/60	35/5594	0.04751258

**Table S15: Significantly enriched Reactome pathways in MKN1 cells after 24 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
1989781	PPARA activates gene expression	7/180	35/5594	0.04242702

**Table S16: Significantly enriched KEGG pathways in MKN7 cells after 4 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
hsa01522	Endocrine resistance	9/157	90/5844	0.0337614
hsa04668	TNF signaling pathway	10/157	102/5844	0.02646242
hsa04060	Cytokine-cytokine receptor interaction	16/157	186/5844	0.00355486
hsa04630	Jak-STAT signaling pathway	14/157	125/5844	0.00112593

**Table S17: Significantly enriched KEGG pathways in MKN7 cells after 24 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
hsa03008	Ribosome biogenesis in eukaryotes	25/785	69/5844	0.00039694
hsa04110	Cell cycle	33/785	118/5844	0.0030143
hsa03030	DNA replication	13/785	33/5844	0.01815882

**Table S18: Significantly enriched Reactome pathways in MKN7 cells after 24 h afatinib treatment.**

ID	Description	GeneRatio	BgRatio	p.adjust
453279	Mitotic G1-G1/S phases	40/764	114/5594	3.6681E-06
69278	Cell Cycle, Mitotic	91/764	380/5594	6.4007E-06
69206	G1/S Transition	34/764	94/5594	7.6198E-06
113510	E2F mediated regulation of DNA replication	16/764	28/5594	1.4565E-05
1640170	Cell Cycle	103/764	462/5594	1.4565E-05
69306	DNA Replication	32/764	92/5594	2.8265E-05
69205	G1/S-Specific Transcription	10/764	13/5594	5.269E-05
69190	DNA strand elongation	16/764	31/5594	5.6795E-05
69242	S Phase	35/764	110/5594	6.0213E-05
176187	Activation of ATR in response to replication stress	17/764	35/5594	6.1092E-05
69481	G2/M Checkpoints	20/764	49/5594	0.00018433
69239	Synthesis of DNA	29/764	88/5594	0.000189
68962	Activation of the pre-replicative complex	14/764	28/5594	0.00029987
68877	Mitotic Prometaphase	29/764	91/5594	0.00034588
2500257	Resolution of Sister Chromatid Cohesion	27/764	85/5594	0.00072655
69620	Cell Cycle Checkpoints	33/764	116/5594	0.00105427
180786	Extension of Telomeres	12/764	24/5594	0.00113179
68874	M/G1 Transition	23/764	72/5594	0.0022782
69002	DNA Replication Pre-Initiation	23/764	72/5594	0.0022782
73886	Chromosome Maintenance	22/764	69/5594	0.00325081
2555396	Mitotic Metaphase and Anaphase	37/764	149/5594	0.0064384
176974	Unwinding of DNA	7/764	11/5594	0.00668213
73817	Purine ribonucleoside monophosphate biosynthesis	7/764	11/5594	0.00668213
2467813	Separation of Sister Chromatids	35/764	141/5594	0.00851589
174417	Telomere C-strand (Lagging Strand) Synthesis	10/764	22/5594	0.00996357
68882	Mitotic Anaphase	36/764	148/5594	0.00996357
69186	Lagging Strand Synthesis	9/764	20/5594	0.02130541

<b>15869</b>	Metabolism of nucleotides	21/764	75/5594	0.02459538
<b>113507</b>	E2F-enabled inhibition of pre-replication complex formation	6/764	10/5594	0.02513251
<b>68886</b>	M Phase	46/764	216/5594	0.03263143
<b>69300</b>	Removal of licensing factors from origins	18/764	64/5594	0.04742088
<b>69304</b>	Regulation of DNA replication	18/764	64/5594	0.04742088

**Table S19: Regulated genes after afatinib and trastuzumab + afatinib treatment related to the biological function “positive regulation of cell motility”.** In MKN1 cells regulated genes are colored in blue.

MKN1 4h Afa vs. MKN1 4h untr	MKN1 4h Tra+Afa vs. MKN1 4h untr	MKN7 4h Afa vs. MKN7 4h untr	MKN7 4h Tra+Afa vs. MKN7 4h untr	NCI-N87 4h Afa vs. NCI-N87 4h untr	NCI-N87 4h Tra+Afa vs. NCI-N87 4h untr
<i>CCR7</i>	<i>CXCL1</i>	<i>ACKR3</i>	<i>SEMA7A</i>	<i>ARHGEF2</i>	<i>ARHGEF2</i>
<i>CXCL1</i>	<i>CXCL8</i>	<i>ADAM8</i>	<i>ACKR3</i>	<i>ATOH8</i>	<i>ATOH8</i>
<i>CXCL8</i>	<i>CYR61</i>	<i>ARHGEF2</i>	<i>ADAM8</i>	<i>CXCL1</i>	<i>BCL2</i>
<i>CYR61</i>	<i>ETS1</i>	<i>BCL2</i>	<i>ARHGEF2</i>	<i>CXCL2</i>	<i>CXCL1</i>
<i>ETS1</i>	<i>F2RL1</i>	<i>CCL20</i>	<i>BCL2</i>	<i>CXCL3</i>	<i>CXCL2</i>
<i>F2RL1</i>	<i>F3</i>	<i>CD274</i>	<i>CCL20</i>	<i>CXCL8</i>	<i>CXCL3</i>
<i>F3</i>	<i>HAS2</i>	<i>DRD1</i>	<i>CD274</i>	<i>EDN2</i>	<i>CXCL8</i>
<i>HAS2</i>	<i>HBEGF</i>	<i>ETS1</i>	<i>CXCL12</i>	<i>F3</i>	<i>EDN2</i>
<i>HBEGF</i>	<i>ITGA2</i>	<i>FLT1</i>	<i>DRD1</i>	<i>GRB7</i>	<i>ENPP2</i>
<i>IL1B</i>	<i>PLPP3</i>	<i>HBEGF</i>	<i>ETS1</i>	<i>HAS2</i>	<i>F3</i>
<i>ITGA2</i>	<i>PTGS2</i>	<i>ITGA2</i>	<i>HBEGF</i>	<i>HBEGF</i>	<i>GRB7</i>
<i>PDGFB</i>	<i>SEMA6D</i>	<i>NRP1</i>	<i>ITGA2</i>	<i>HMCN2</i>	<i>HAS2</i>
<i>PLPP3</i>	<i>SERPINE1</i>	<i>PTAFR</i>	<i>LEF1</i>	<i>NOS3</i>	<i>HBEGF</i>
<i>PTGS2</i>	<i>SPRY2</i>	<i>PTGS2</i>	<i>MADCAM1</i>	<i>RHOB</i>	<i>ITGA2</i>
<i>SEMA6D</i>	<i>TNFSF14</i>	<i>PTK2B</i>	<i>NRP1</i>	<i>SNAI1</i>	<i>JCAD</i>
<i>SERPINE1</i>		<i>SEMA4B</i>	<i>PTGS2</i>	<i>SPRY2</i>	<i>NOS3</i>
<i>SPRY2</i>		<i>SEMA7A</i>	<i>PTK2B</i>	<i>ZC3H12A</i>	<i>RHOB</i>
<i>VEGFC</i>		<i>SERPINE1</i>	<i>SEMA4B</i>		<i>SNAI1</i>
		<i>SMURF2</i>	<i>SERPINE1</i>		<i>SPRY2</i>
		<i>SPRY2</i>	<i>SMURF2</i>		
		<i>VEGFD</i>	<i>SPRY2</i>		
			<i>TERT</i>		

**Table S20: Regulated genes after afatinib and trastuzumab + afatinib treatment related to the biological function “positive regulation of apoptotic signaling pathway”. In NCI-N87 cells exclusively regulated genes are colored in blue.**

MKN1 24h Cet vs. MKN1 24h untr	MKN1 24h Afa vs. MKN1 24h untr	MKN1 24h Tra+Afa vs. MKN1 24h untr	MKN7 24h Afa vs. MKN7 24h untr	MKN7 24h Tra+Afa vs. MKN7 24h untr	NCI-N87 24h Afa vs. NCI-N87 24h untr	NCI-N87 24h Tra+Afa vs. NCI-N87 24h untr
<i>BMF</i>	<i>AGT</i>	<i>ATF3</i>	<i>BCL2</i>	<i>BCL2</i>	<i>BAX</i>	<i>BAX</i>
<i>TNFSF10</i>	<i>ATF3</i>	<i>BCL2</i>	<i>BCL2L1</i>	<i>BCL2L1</i>	<i>BBC3</i>	<i>BBC3</i>
	<i>BCL2</i>	<i>BMF</i>	<i>BID</i>	<i>BID</i>	<i>BCL2</i>	<i>BCL2</i>
	<i>BMF</i>	<i>TNFRSF12A</i>	<i>CTSC</i>	<i>CTSC</i>	<i>BCL2L1</i>	<i>BCL2L1</i>
	<i>TNFSF10</i>	<i>TNFSF10</i>	<i>FAM162A</i>	<i>FAM162A</i>	<i>BCLAF1</i>	<i>BCLAF1</i>
			<i>HRK</i>	<i>HRK</i>	<i>BID</i>	<i>BID</i>
			<i>MMP9</i>	<i>MMP9</i>	<i>BMF</i>	<i>BMF</i>
			<i>PLA2G6</i>	<i>NOX1</i>	<i>CAV1</i>	<i>CAV1</i>
			<i>PLAUR</i>	<i>PLA2G6</i>	<i>CTSC</i>	<i>CTSC</i>
			<i>S100A9</i>	<i>PLAUR</i>	<i>E2F1</i>	<i>DYNLL1</i>
			<i>SFRP1</i>	<i>PMAIP1</i>	<i>FADD</i>	<i>DYNLL2</i>
			<i>TFAP4</i>	<i>S100A9</i>	<i>FAF1</i>	<i>E2F1</i>
			<i>TFDP1</i>	<i>SFRP1</i>	<i>FAS</i>	<i>FADD</i>
			<i>TNFRSF10A</i>	<i>TFAP4</i>	<i>GSN</i>	<i>FAF1</i>
			<i>TNFRSF10B</i>	<i>TFDP1</i>	<i>HYAL2</i>	<i>FAM162A</i>
				<i>TNFRSF10A</i>	<i>IL19</i>	<i>FAS</i>
				<i>TNFRSF10B</i>	<i>IL20RA</i>	<i>GSK3A</i>
					<i>INHBB</i>	<i>GSN</i>
					<i>LCK</i>	<i>HYAL2</i>
					<i>LGALS9</i>	<i>IFNB1</i>
					<i>MMP9</i>	<i>IL19</i>
					<i>NACC2</i>	<i>IL20RA</i>
					<i>NF1</i>	<i>INHBB</i>
					<i>NFATC4</i>	<i>LCK</i>
					<i>NKX3-1</i>	<i>LGALS9</i>
					<i>PAK2</i>	<i>LTBR</i>
					<i>PARK7</i>	<i>MAL</i>
					<i>PDCD5</i>	<i>NACC2</i>
					<i>PDIA3</i>	<i>NF1</i>
					<i>PEA15</i>	<i>NFATC4</i>
					<i>PINK1</i>	<i>NKX3-1</i>
					<i>PLA2G6</i>	<i>NMT1</i>
					<i>PLAUR</i>	<i>NOX1</i>
					<i>PMAIP1</i>	<i>PAK2</i>
					<i>PPIF</i>	<i>PARK7</i>
					<i>PPP2R1B</i>	<i>PDCD5</i>
					<i>PPP3CC</i>	<i>PDIA3</i>
					<i>PRKRA</i>	<i>PEA15</i>
					<i>RIPK3</i>	<i>PLA2G6</i>

	<i>SFN</i>	<i>PLAUR</i>
	<i>SFPQ</i>	<i>PMAIP1</i>
	<i>SKIL</i>	<i>PPIF</i>
	<i>SLC9A3R1</i>	<i>PPP1CA</i>
	<i>SMAD3</i>	<i>PPP2R1B</i>
	<i>STK4</i>	<i>PPP3CC</i>
	<i>TFAP4</i>	<i>PRKRA</i>
	<i>TFDP1</i>	<i>S100A9</i>
	<i>TGFBR1</i>	<i>SFN</i>
	<i>TNFRSF10A</i>	<i>SFPQ</i>
	<i>TNFRSF10B</i>	<i>SIRT1</i>
	<i>TNFRSF12A</i>	<i>SKIL</i>
	<i>TNFSF10</i>	<i>SLC9A3R1</i>
	<i>TP73</i>	<i>SMAD3</i>
	<i>TPD52L1</i>	<i>STK4</i>
	<i>WDR35</i>	<i>TFAP4</i>
	<i>YWHAB</i>	<i>TFDP1</i>
	<i>YWHAE</i>	<i>TGFBR1</i>
	<i>YWHAG</i>	<i>TNFRSF10A</i>
	<i>YWHAH</i>	<i>TNFRSF10B</i>
	<i>YWHAQ</i>	<i>TNFRSF12A</i>
	<i>YWHAZ</i>	<i>TNFSF10</i>
	<i>ZNF205</i>	<i>TP63</i>
		<i>TP73</i>
		<i>TPD52L1</i>
		<i>WDR35</i>
		<i>YWHAB</i>
		<i>YWHAE</i>
		<i>YWHAG</i>
		<i>YWHAH</i>
		<i>YWHAQ</i>
		<i>YWHAZ</i>
		<i>ZNF205</i>