

Supplementary Tables

Table S1. Primer sequences for randomized siRNA library generation/screening, and pre-designed siRNAs directed against the TNFRSF1B and KCNQ1OT1 transcripts.

Primer Sequences		
Name	Sequence (5' → 3')	Number of Nt
Clal/NotI F	CCGCGCATCGATGCGGCCGCCAAGGTCGGGCAGGAAGAGGGCCTA	45
EcoRI-H1 R	CGCGAATTCGAACGCTGACGTCATCAACCCGCTCCAAGGAATCGC	45
BamHI-MluI-siRNA(EGFP)-SmaI R	GCGCGGATCACGCGTAAAACTTCAGGGTCAGCTT-GCCGTTTTTCCCGGGCTTTCCACAA	60
pLIB-N R	TGTGGAAAGCCCCGGGAAAAAGNNNNNNNNNNNNNNNNNNNTTTTAC-GCGTGTCTCATACAGAACTTATAAGAT	73
pCI-neo(CMV-)LIB F	TTCAAGAACTCTGTAGCACC GCCT	24
pJET 1.2 F	CGACTCACTATAGGGAGAGCGGC	23
pJET 1.2 R	AAGAACATCGATTTTCCATGGCAG	24
Pre-designed siRNAs		
siRNA name	Sequence (5' → 3')	
ON-TARGET plus Non-targeting siRNA (C-)	UGGUUUACAUGUCGACUAA	
TNFRSF1B		
ON-TARGET plus SMART pool siRNA J-003934-05 (siRNA1)	CGACUUCGCUCUUC CAGUU	
ON-TARGET plus SMART pool siRNA J-003934-06 (siRNA2)	GGAAUGUGCCUUUCGGUCA	
ON-TARGET plus SMART pool siRNA J-003934-07 (siRNA3)	CAUCAGACGUGGUGUGCAA	
ON-TARGET plus SMART pool siRNA J-003934-08 (siRNA4)	AGCCUUGGGUCUACUAAUA	
KCNQ1OT1		
Lincode SMART pool siRNA N-188025-01 (siRNA1)	GCCAAGAACCAACGAAUGA	
Lincode SMART pool siRNA N-188025-02 (siRNA2)	GCAUAUCUGUCUUC CGUAU	
Lincode SMART pool siRNA N-188025-03 (siRNA3)	GAAUACAGAGAACGGCUGA	
Lincode SMART pool siRNA N-188025-04 (siRNA4)	GAAUACAUAAGCACGAUU	

Table S2. List of the final 167 siRNA sequences obtained through randomized siRNA library screening in 6CFSMEo- cells.

siRNA_id *	siRNA_seq (5' → 3')	siRNA_id	siRNA_seq (5' → 3')
1	GTATACCCTGTACTAGTTG	92	GAGGGTGATGTTTGCTGG
2	GGCATTGGCCTATTGGTAT	93	GGGATCGATACCACTACTT
3	GAGCGAGCTACGGGACTCT	94	GGCTCTGTGTATGTAAGTC
4	GTGGGCCAGCGTACTTTC	95	GGCTGGTCATAACCTCTCT
5	GCGTTATGGTGTTGGTAAC	96	GACGTGAACGAAAGACTTA
6	GGTTAATCAAATTGGTGGA	97	GGATCGATCTACGCACAGT
7	GCGCACGGGGCGCTAGTTT	98	GGTTCTTCGTACTATTGGC
8	GGGTGCGTGGGCAGTGTGT	99	GTAAAGCATAGGATGATAA
9	GTGAGAGTGAGCGTTTATC	100	GCACATGAGGGATGCAACA
10	GTGACTTGCTTGGTACTTC	101	GGTTGCTGCGAGCTGCCAC
11	GAGCAACATACCAGTGTCTG	102	GAGAGTCGGAGGTACTTGC
12	GGCTCGTCACCCGTGAATC	103	GACTTTAGGACGTGCATCG
13	GAGTCTAGATAGTGTTC	104	GCACTTTATGTTCCGCTCC
14	GTGCCAGTAAGGCCGTACC	105	GGCCGGTCGGTTCTCGGTC
15	GTCGTGCTAATGAGGATTA	106	GTATTAAGGGCGATCCGTA
17	GGCGATAGAGTTGTGCGCG	107	GGGTTGCACCGCTTTCTAC
18	GTTTGCTGGCTACTCCTTT	108	GCGTGGTTCACGCTGTCCA
19	GAGGCTTGCGTGCTGGACC	109	GATGCTTGCAAGAATAATT
20	GTGTTTTCCATGTGCTTTA	110	GGGTCATGGGGGCTGCGCA
21	GCATCTGTCATGCATACTC	111	GGTCTGTGCAACCAACAAT
22	GTCGGTATGGCTAGTTACG	112	GGTCTATTTGGCATAGTAT
23	GTATGGTCAACACAGTTCC	113	GTGAGATGTAGCATATCTG
24	GCGGCAAGCTGACCCGTAA	114	GACCCGTACGTGTGATC
25	GTTTAAGGTTGCAGTT	115	GTGAGGGTTAGTCTCGTTC
26	GGCAATGATACTTATCCTA	116	GGCATATGGTTCGGTCTGGT
27	GGGTTACTTATCATGAACC	117	GCACGTCTCGGAGCAGGTG
28	GTCGCAGTCTGCATTTTGC	118	GATCGCCACACGATTTCGCT

29	GTCTTCGCCATGATTCTGG	119	GGATGGTCCTTAATCGTTA
30	GGCTCGACTGAGGTGTGGA	120	GTCACGCCGCTACGCACCG
31	GCGATACCTCCCTACGCC	121	GGATGTGCTATATCTGGGA
32	GTCTGAGAAATACTTTCGA	122	GTTGCTGGGAGCCTTCCCC
33	GATAGTCTGGGCCAATATC	123	GGGTAATTGAGTCGACGTC
34	GCGGTTTTCGATTGGGCGG	124	GAACCGGTCTGGCTACAAC
35	GGTGCCACGATATCTGAAG	125	GTAACGTGGCGCGGGTACA
36	GGTGTGTGTTTTCTACCTT	126	GATGCAACCTGGTTTTTAC
37	GGCGTGTCTGGGATGTTCCC	127	GGCGCTAAGGTAGCCTCAT
38	GGCAACGCTGTGGTAATAC	128	GACGCTGCCCCGCCACCGT
39	GCATTTTCGTCTTCTTGGG	130	GACAGGATAGGATTCCCTC
40	GCTCGCGCGAAATGAGTGA	131	GGAACAATGGTCTCATGTC
43	GCGCGACGGGTCTTATCGT	132	GGCCAGCCCTCGGCTTCGT
44	GATATCTTGTGCCTGTCTGT	133	GACGGAACCAATTTACGTG
45	GCGTCTTTTTTGAATGCGC	134	GATGCTACGGGTTTGGTAT
47	GGTGATCTGCTGGCTTACT	135	GAATGACAGGGTCAGTATA
48	GGCTCAGTGGATTATCATT	136	GGAAGGCCAGTTTTCGTTG
49	GTTGCTCCAACATTACATG	137	GATAGAAGTGGTATTTGGC
50	GTTGACAGGAACATAATAA	138	GTGTGGGATTATCAAAACC
51	GTGCTGGTTCAAATAGTTT	139	GACGTCATGGGTTTCCGTT
52	GGTCTTATCAACGTCATGC	141	GCCCTCTCCCTTTGAGCCA
53	GCCTAATAGTGTAGTCAAC	142	GCGAATGGGAATTTCCCTCT
54	GTGCCAGAATGTGGTGCAC	144	GGCAACAAAGAGGTAATAC
55	GGAATGAGGGGACGGAGAG	145	GCGGGTTTGTGTCTACTGT
56	GGGTGTTCAAACAAATAAG	146	GTCTGCCTCACTTACTATA
58	GATAAGCACCCCAATTGAG	147	GGGGAGGGCATGTTATAGA
59	GTGTTTCCGGGGGTAAGGA	148	GGTATGACGGCGTGATCAA
60	GCTGGTTCCTGCTTCTCAT	149	GCCAAGGCACCCC
61	GTGGAAATTTTCGAGTCGCG	150	GGCCAATAGGGTATCGCAC
62	GCTCGCCTGGTCGGACAGC	151	GGTGACAATACAGTTCATA
63	GTTGGGTGTACTGGTCCCT	152	GAGTGACCGCGCACAAATGC
64	GCGTGCGATGTTTACAGTG	153	GATCGCTTGATGGGCTAGG
65	GGAAGTGGACTCACCCCTT	154	GCGGCCAGCTCCTCTATGC
66	GGGCATGAACAGTCCTTAG	155	GGTTGGTGGGTGGGACGCG
68	GCGCGTGTCTTACGTTTT	156	GATACATTGGTTTTTCGCCC
69	GCGTAATTTGGGGATACGA	157	GCGCTACTTACGGTCTTAT
70	GACTGCTTCTATTTGACAA	159	GACGCCGTAAAGTGCCCGA
71	GTAGCAACTCTGGCGTAGT	160	GTGTAAGCTATTTGTGTAC
72	GGTCGGCAGTAAGCAGTGA	161	GTGGTATCTCTGGTTCCTC
73	GCCCATTCGCTCTTGTTCA	162	GGTTACCGCGTCATCTATG
74	GGCTCCTTACGCGTAATGC	163	GTAGTAGAGATGTAAGTGG
75	GGTAAATCTTCCCTATCGG	164	GTGTCATTCATCTCGTGTG
78	GTGCGTGGGTAGCTCTTTC	165	GCTTACGTTTTGTGCTATG
79	GTGACACAGCCTACTAGCT	167	GGACGCTTCGTGCGAGACG
80	GGTGGTAATGAGGTCGTCT	168	GTATTACCGTGTCTTTATC
81	GGTCCGCAACACCGCGATA	169	GAGCTTTAGTCGCGTGTCT
82	GCCTCATGGCCAACATGTC	170	GGTGGTCCCTCCCTCCTCC
83	GCGTGATGGGCCCTAAATG	172	GTTGTCCTTCTGCCAGAA
84	GGGAGGGCTGGTCTTATGT	173	GTTGTCCTACCGGTATTA
85	GGTTGTAGCTCAATTGTGT	174	GTAAACCACTGAGATGGT
86	GGCTGACCAGTCCGCTTTT	175	GGTAGGACCGAAAACGTAT
87	GCTGGATGTCAGTCTATAT	176	GGAGTGTATGTTGCTATCG
88	GGTCTCAATACGCTTCTGT	177	GGATTTTAGGCTCCCGTCC
89	GGGGATACAAAGTCCTCGT	178	GCAAGGTCGGTAAGTGTCT
90	GGAGGACGTGCTTCGGGGA	179	GGTGTGTGCTTGCCCTCG
91	GTTTTGCCTAACGTGTCTGT	180	GGTTCACGCGCGAAATCGT
		181	GGAGTAAAGATACTATCGC

* Clones siRNA 46 and 171 were discarded because they did confer no or marginal survival, respectively, compared to control pEGFP-N1-transfected cells. Clones 129, 143, and 158 and 166 were further discarded because their complete target alignment was < 68 % and/or they presented a centered mismatch with its homologous target. Clones 16, 41, 42, 57, 67, 76, 77, and 140 had no effect size.

Table S3. Number of overrepresented pathways and terms from the built protein-protein interaction (PPI) networks or corresponding Largest Connected Components (LCC). Common overrepresented pathways among the three analyzed cases are quantified.

Database.	Adding Direct Interactors (1 st shell)		Adding Indirect Interactors (2 nd shell) Very High Confident Interactions*	Common Overrepresented Pathways or Terms
	High Confident Interactions*	Very High Confident Interactions		
KEGG Pathways	52	15	32	10
Reactome	258	123	442	91
Biology Process	423	203	474	137
The Gene Ontology Molecular Function	89	64	132	30
Cellular Component	167	102	215	75

* Overrepresented pathways and terms were obtained from the list of genes composing the LCC for the different explored PPIs (FDR adjusted p -value < 0.05). KEGG Pathways, Reactome and The Gene Ontology databases were independently considered.