SUPPLEMENTARY MATERIAL

Focused CRISPR-Cas9 genetic screening reveals USO1 as a vulnerability in B-cell acute lymphoblastic leukemia

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Figure S1

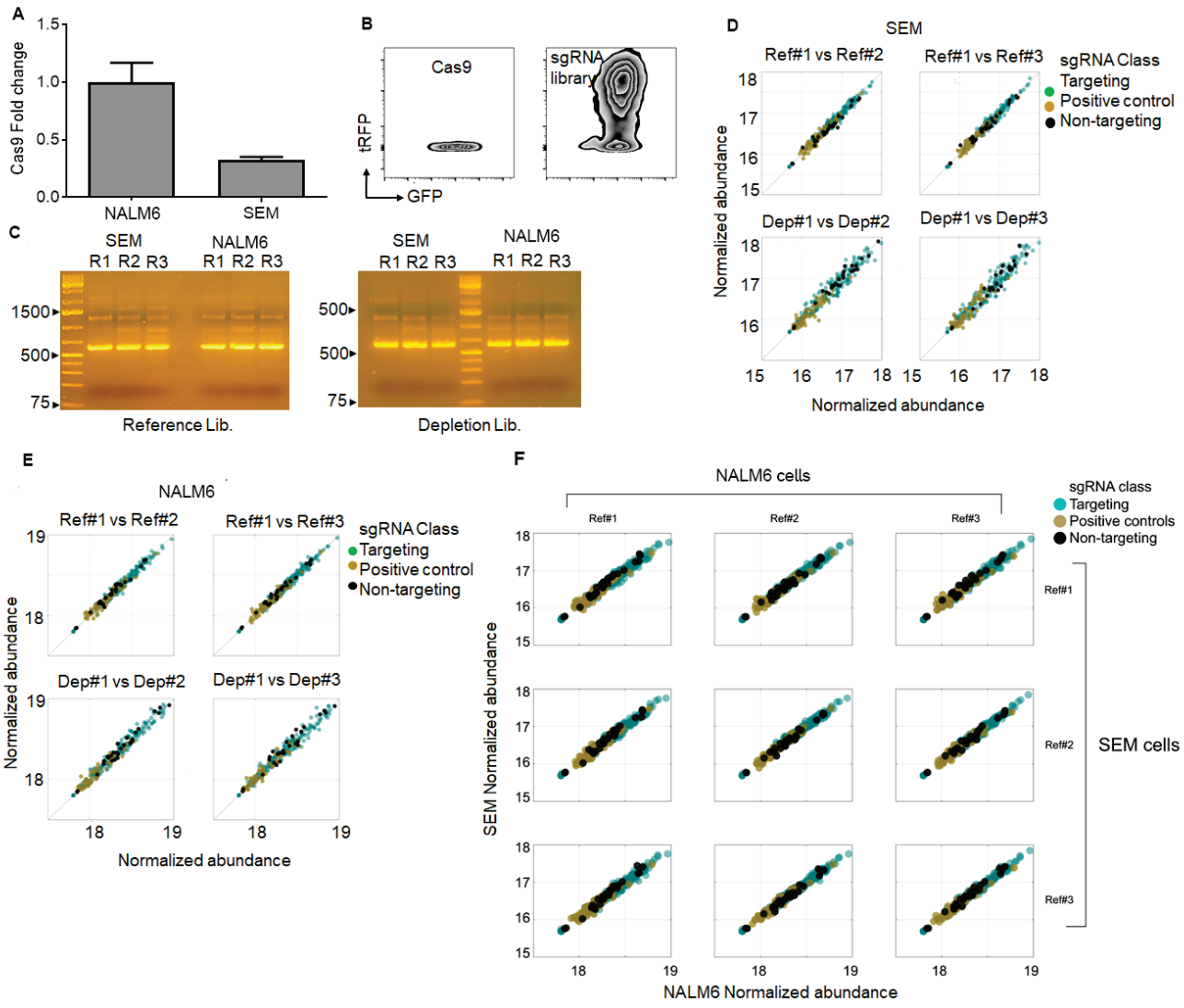


Figure S1. Sub-genomic CRISPR screen preparation. **A**. Cas9 expression in B-ALL cell line NALM6 and SEM prior to CRISPR screen. **B**. FACS plot showing transduction of NALM6 Cas9.EGFP with the undiluted lentiviral vector library, demonstrating effective production of virus with a high titer. **C**. Library preparation from the genomic DNA isolated from the sorted cells as Reference library and from expanded cells for 4 weeks as Depletion library. **D-E.** Intra-cell line Correlation plot of individual sgRNA variance-stabilized abundances in the reference and depletion libraries prepared in SEM and NALM6 cell lines between biological replicates. **F.** Inter-cell line correlation plots of individual sgRNA variance-stabilized abundances in the reference and depletion libraries prepared in SEM and NALM6 cell lines between biological replicates.

Figure S2

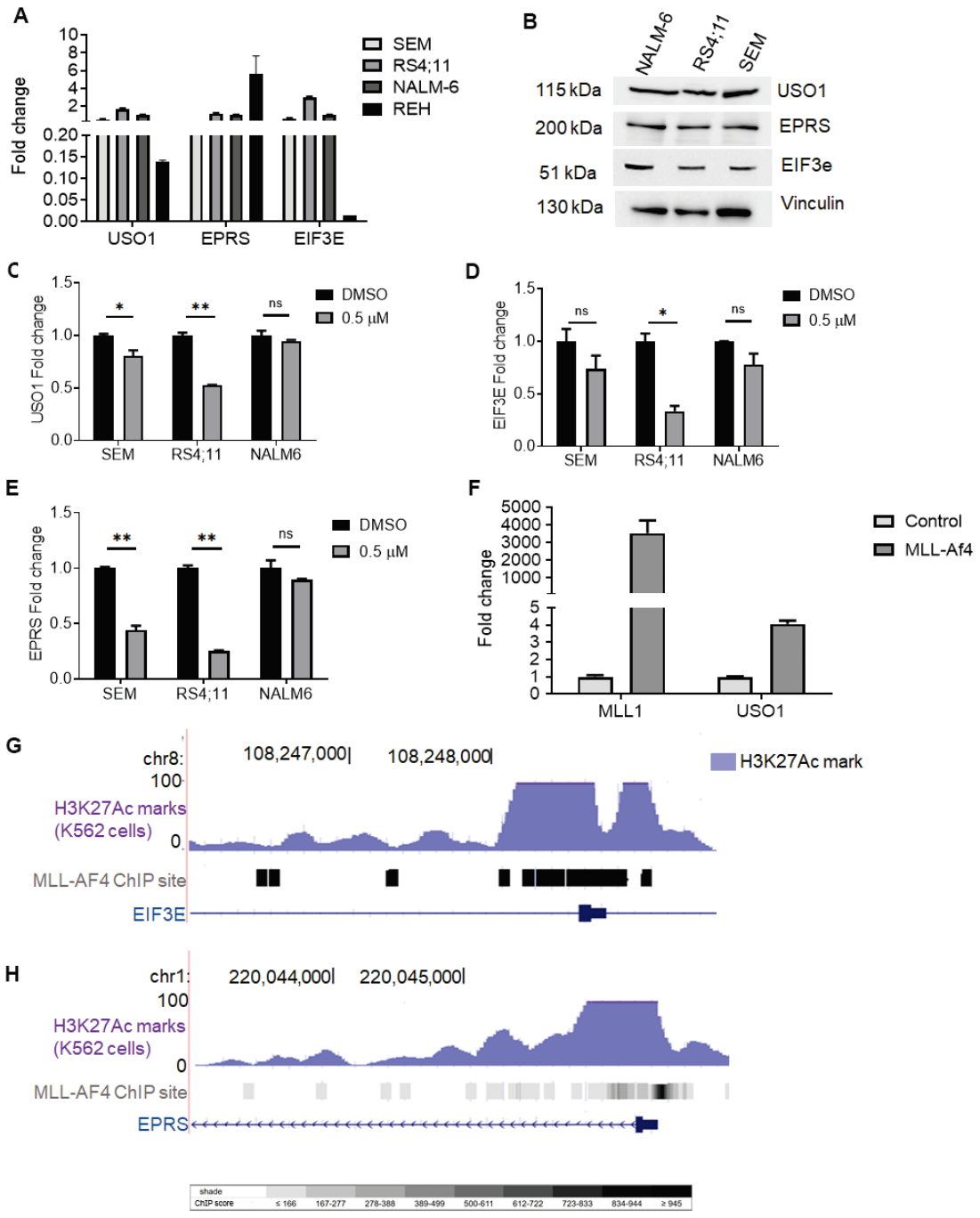


Figure S2. RBP genes expression in B-ALL cell lines. A. mRNA expression of RBP genes identified, measured by RT-qPCR (*USO1, EIF3E* and *EPRS*). Data was normalized to 18S expression level and is represented as fold-change from SEM cells, which are arbitrarily assigned a fold-change of 1. Cell lines examined include SEM, RS4;11 (carry the MLL-AF4 translocation), and NALM6 and REH (do not carry the MLL-AF4 translocation). **B**. Western blot to study basal level expression of *USO1, EIF3E* and *EPRS* in NALM6, SEM and RS4;11cells. **C-E.** RT-qPCR analysis of expression of USO1 (C), EIF3E (D), and EPRS (E) in SEM, RS4;11 and NALM6 cells treated with 0.5 µM EPZ5676. **F.** RT-qPCR analysis of USO1 in murine bone marrow cells with overexpression of MLL-Af4 (control versus MLL-AF4 bars). **G-H.** UCSC genome browser shots of the EIF3E and EPRS loci showing the *MLL-AF4* ChIP site(s) in the regulatory region as identified from the ChIP-Seq data from Lin *et. al.*(ref #21); *Courtesy: UCSC Genome Browser*). Shown are the H3K27Ac track in hematopoietic K562 cells (Blue), and MLL-AF4 binding sites represented as a grayscale score, with black indicating the highest score/highest number of reads from the dataset.

Figure S3

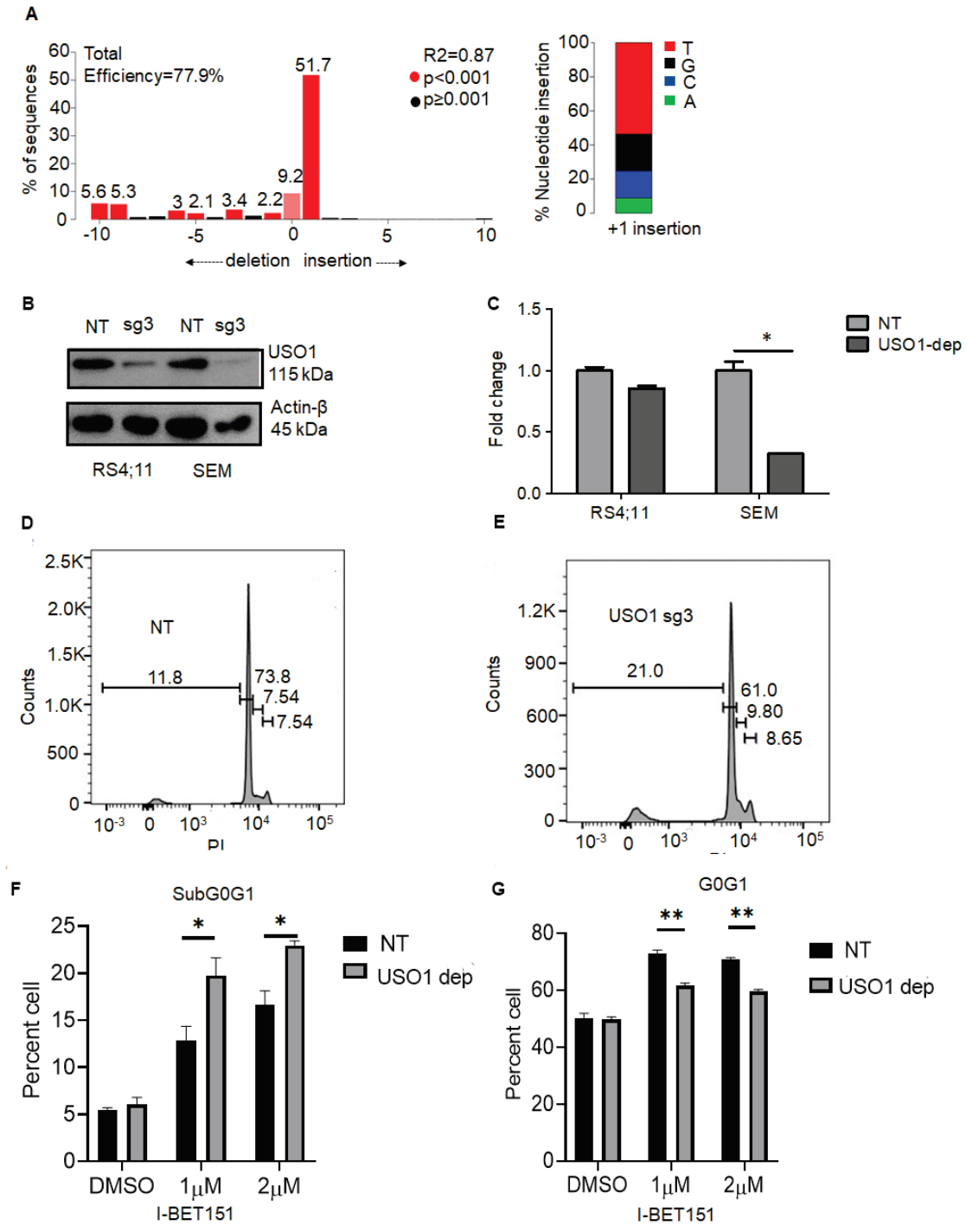


Figure S3. Targeting USO1 in B-ALL cells. A. Plot of insertions and deletions by position near the Cas9 cut site in SEM cells targeted with *USO1* sg3; as determined by Tracking of Indels by Decomposition (TIDE). Genomic sequence aberration is highest immediately adjacent to the cut site (designated as 0). **B**. USO1 depletion by transduction with sg3 in RS4;11 and SEM cells was confirmed by Western blot analysis. **C**. RT-qPCR of USO1 mRNA expression level, expressed as fold-change, in RS4;11 and SEM cells (t-test;*$P < 0.05$). **D-G.** Cell cycle analysis using propidium iodide (PI) of control cells (NT) and USO1-depleted cells (D, E, respectively) following treatment with 1mM I-BET151. F-G. Quantitation of cells from cell cycle analysis in Sub-G0 (F) and G0/G1 (G) at 2 different concentrations of I-BET151(t-test; *P < 0.05, **P< 0.001).

Figure S4

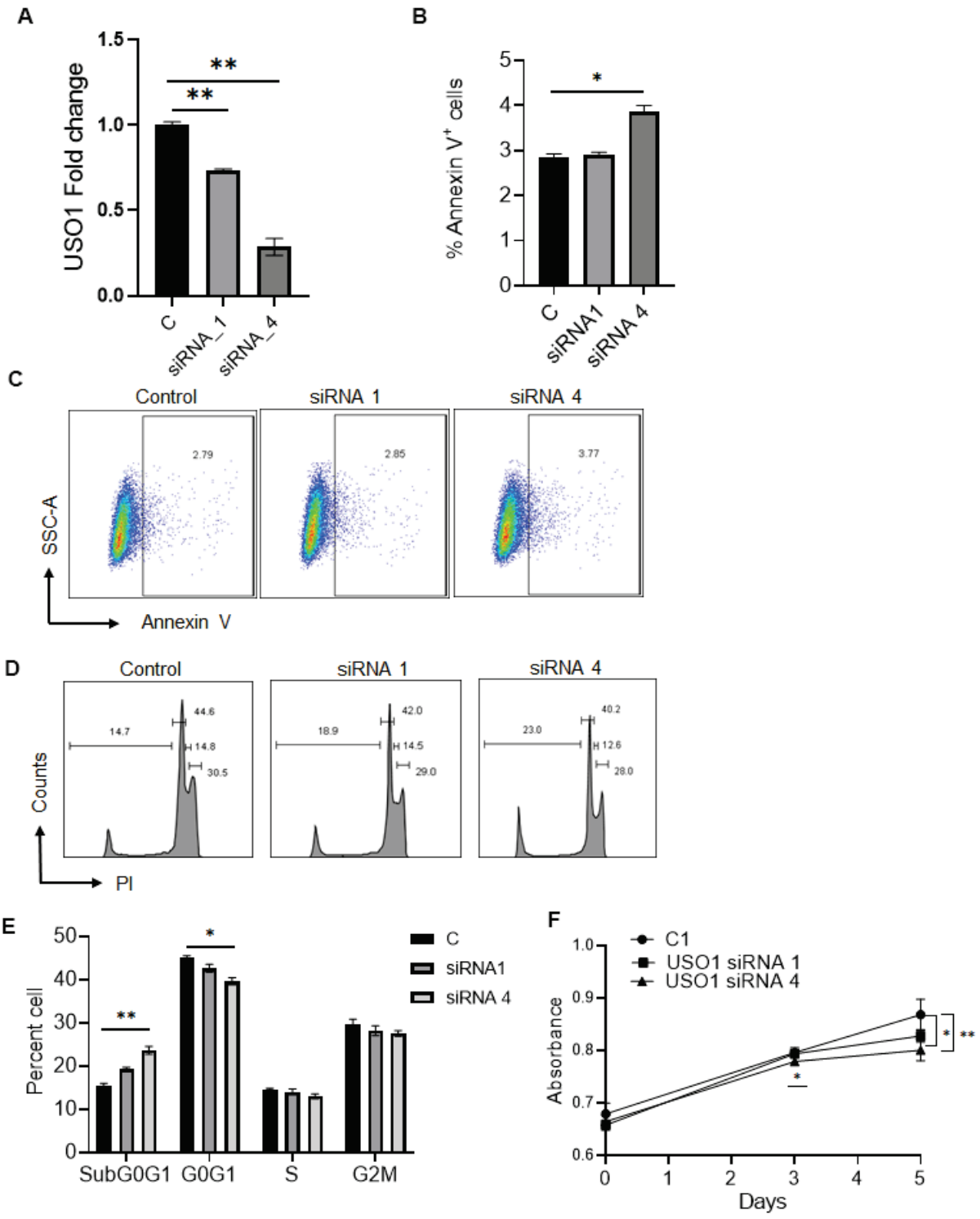


Figure S4. Modulation of USO1 expression by siRNA mediated knockdown. A. RT-qPCR analysis of USO1 expression levels, expressed as fold-change, in SEM cells that were subjected to nucleofection with a control siRNA or siRNA_1 or siRNA_4. **B-C.** Apoptosis induction, as measured by Annexin V staining, in SEM cells that were transduced with USO1-siRNAs. **D-E.** Cell cycle analysis, using propidium iodide staining, of USO1-siRNA-treated cells. **F.** MTS assays (Absorbance at 490nm) measuring the growth over time (days) of USO1-siRNA-treated SEM cells. (T-test; *P < 0.05, **P< 0.001).

Figure S5

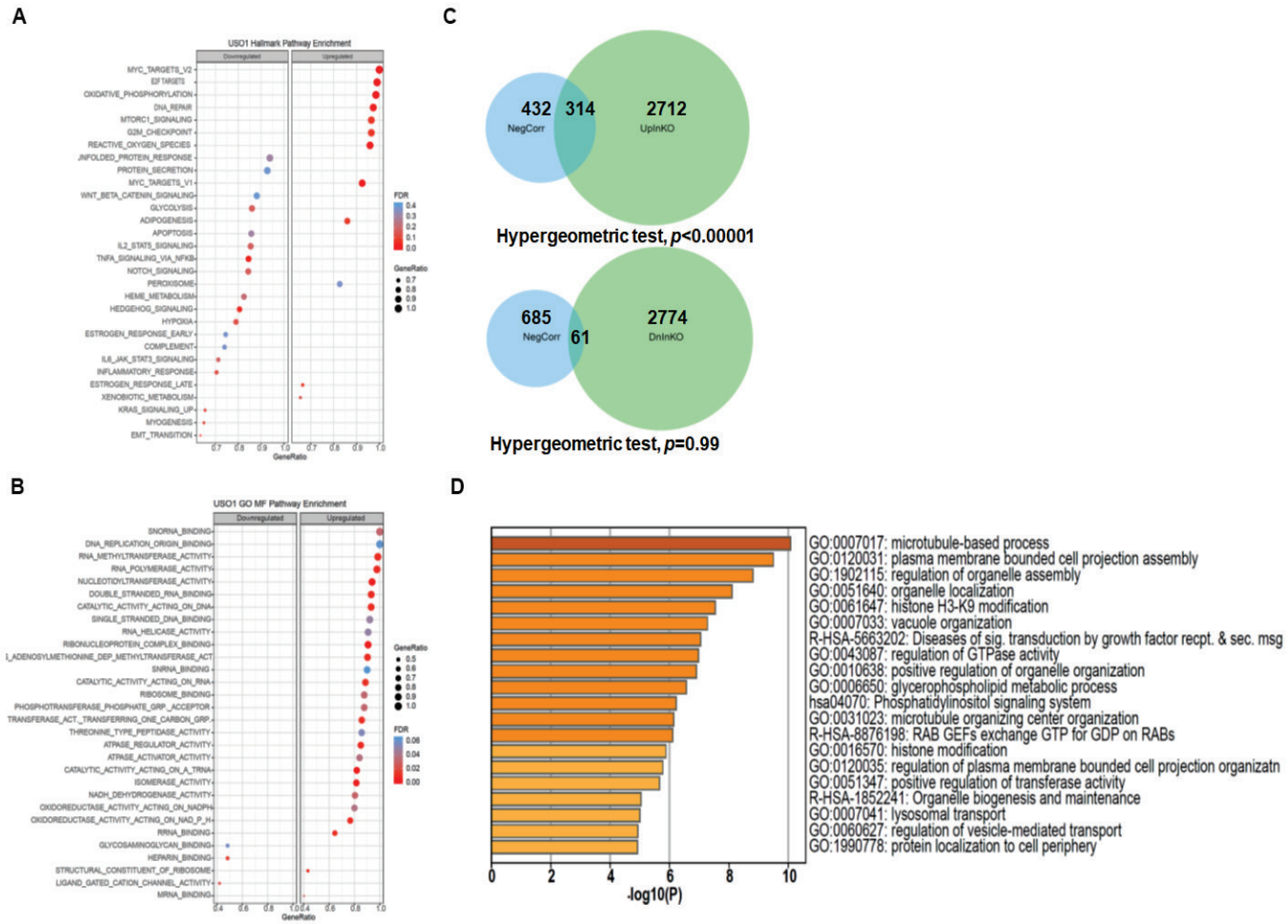


Figure S5. GO Molecular function analysis from RNA-Seq data. A-B. Differential expression analysis of *USO1* depleted SEM cells analyzed by GSEA with msigDB Hallmark gene sets and the GO Molecular function dataset, show enrichment of multiple RNA homeostasis related pathway. **C.** Venn diagrams showing overlap of *USO1*-negatively correlated genes in Target-Phase II ALL dataset with the genes that are significantly downregulated or upregulated in *USO1* depleted SEM cells. See Figure 4 for assumptions utilized in the Hypergeometric test. **D**. Enrichment analysis of the genes downregulated in *USO1* depleted cells that also have a high positive correlation with USO1 using Metascape. The data shows enrichment of several cancer-relevant pathways.

Figure S6

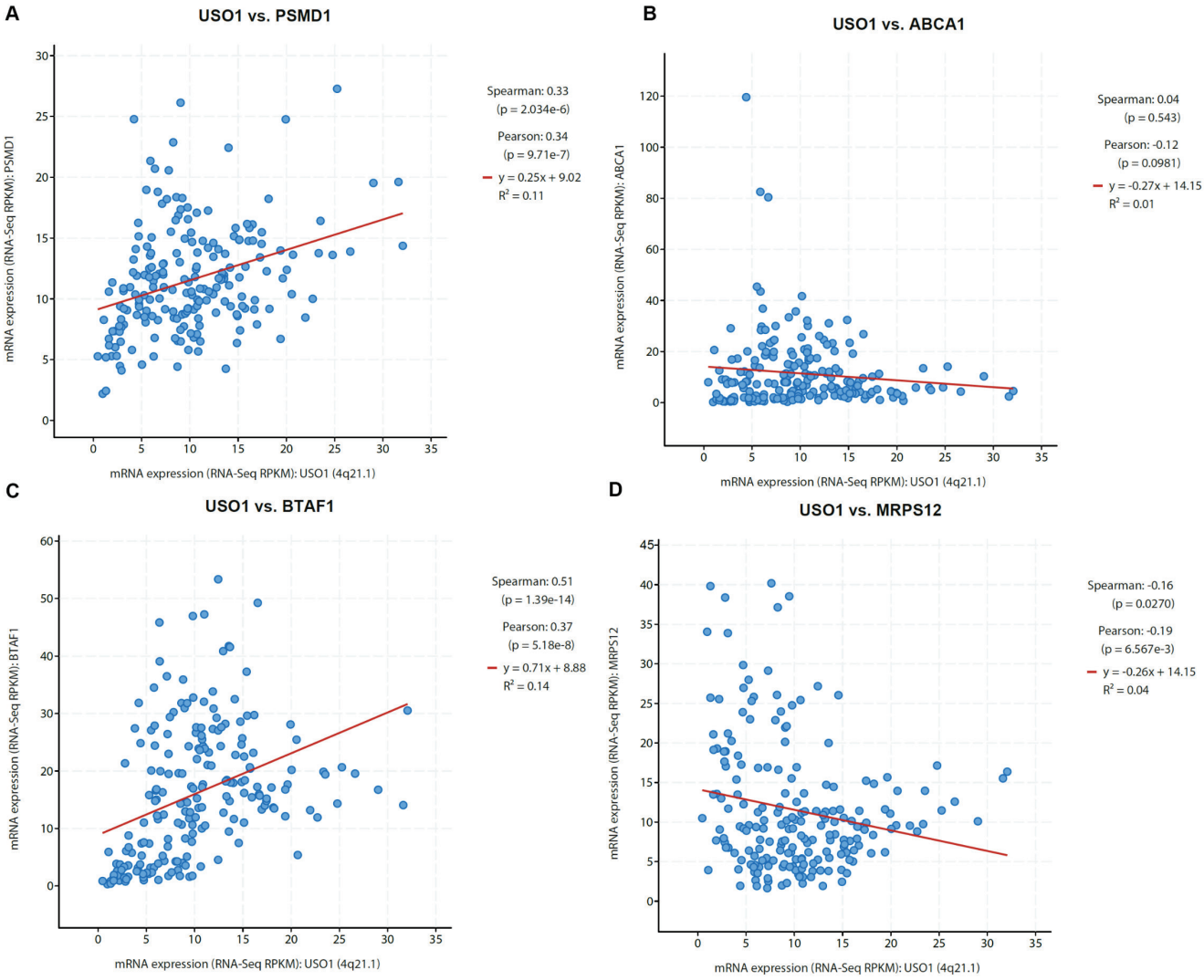
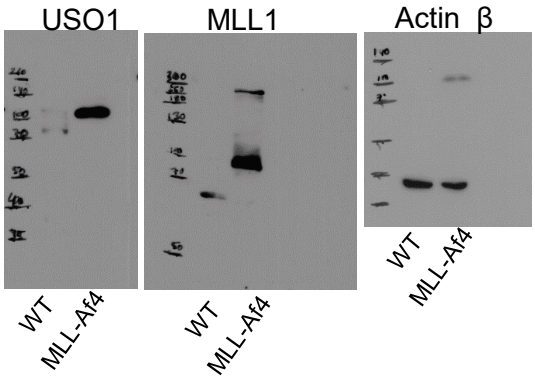
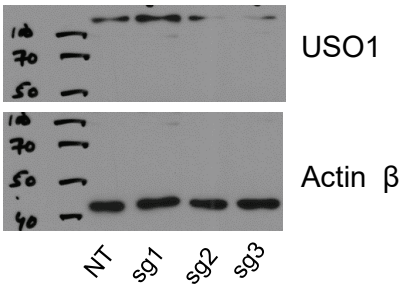


Figure S6. Correlation of USO1 with experimentally downregulated genes following USO1 knockdown. A-D. Genes downregulated in *USO1* depleted SEM, including *PSMD1*, *ABCA1, BTAF1 and MRPS12* show a strong positive correlation with USO1 expression in clinical B-ALL samples (*Courtesy: cBioPortal).*

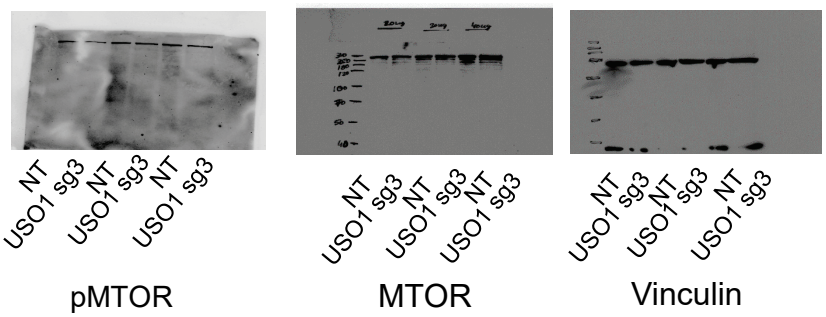
Figure S7a



Corresponding to Fig.2d



Corresponding to Fig.3c



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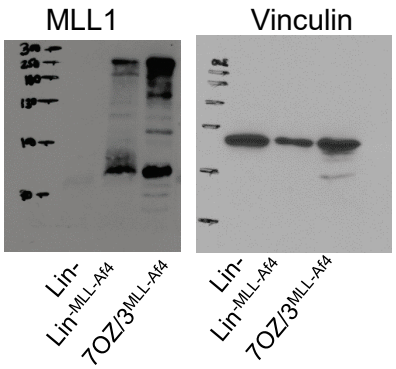

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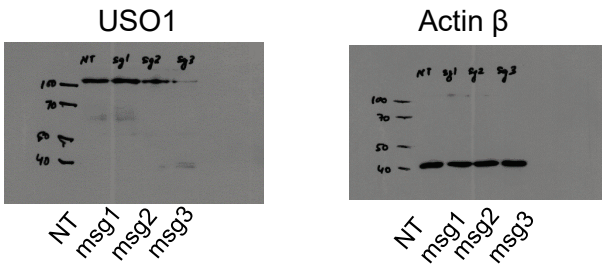

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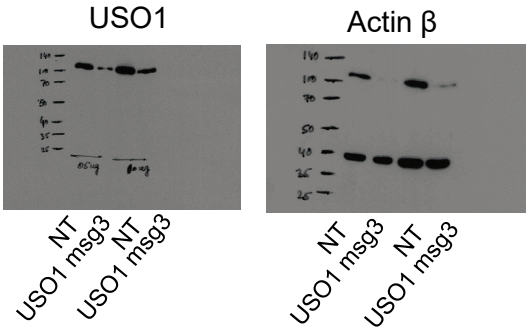
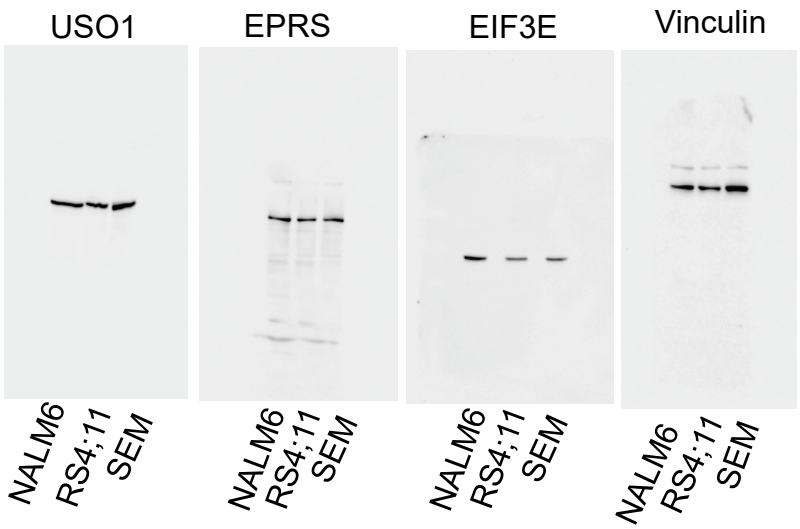


Corresponding to Fig. 5g

Figure S7a. Primary Western Blot Data. Each sub-panel lists the corresponding main panel in the main figures. These panels are the portion of the Western Blot scanned image that corresponds with the experiment being performed. In other cases, panels are showing the portion of a scanned image obtained by imaging on a ChemiDoc Imaging system from Biorad.

Figure S7b



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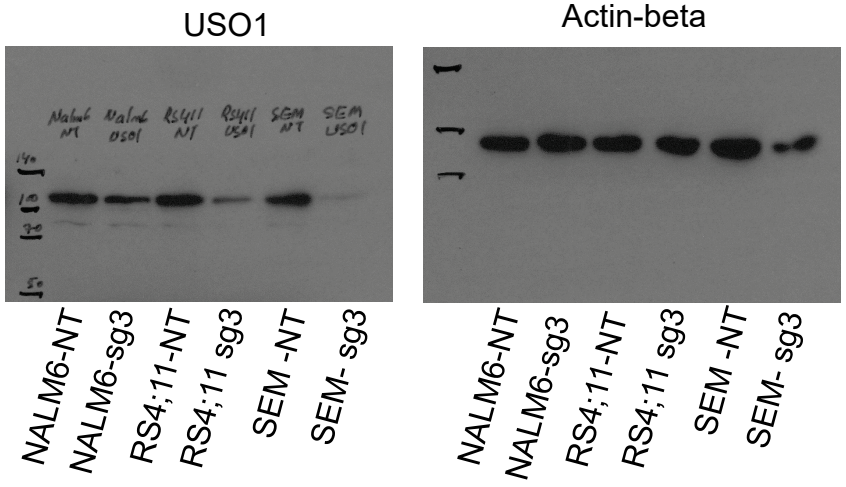

Corresponding to Fig. S3b

Figure S7b. Primary Western Blot Data. Each sub-panel lists the corresponding main panel in the main figures. These panels are the portion of the Western Blot scanned image that corresponds with the experiment being performed. In other cases, panels are showing the portion of a scanned image obtained by imaging on a ChemiDoc Imaging system from Biorad.

Gene Name	Guide RNA sequence
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IGF2BP3	AAGCACCAGATGCTAAAGTG
IGF2BP3	C CAC CGT AAA GAA AAT GCG G
IGF2BP3	A GGC GCA GAG GCA AAT CAC A
IGF2BP3	G CTG GGC GGC CAT TTC ATC A
BAZ1A	C AGT GCA TAA GCC AAA TCG G
BAZ1A	T GGT GTC AAA TCA TAC ACT G
BAZ1A	T CCA GTA TCG TCT ATA CAT G
BAZ1A	G TAA GCG CGA ACG ATG GGT A
BAZ1A	T TTC CTG ATG GAG TAA CCC T
USO1	A GGG TGA TAA GAT CGA CAG A
USO1	G GAC TTA CTA GCG GAT TCC A
USO1	A GCT ACT GGT AGC ACC AGG A
USO1	T CAG CTG GCC AGT TAT TAT G
DDX3Y	TATGAACACCACTACAAGGG
DDX3Y	C AGA TTC GGG ACT TAG AAC G
DDX3Y	C AGT TTA GCG ATA TTG ACA T
DDX3Y	A TGA TAA AGA CAG TTC AGG T
DDX3Y	G TAT ATA TCT GAC TCA GTA T
MBNL1	G TAT GTC GAG AGT ACC AAC G
MBNL1	CAACGTGGCAATTGCAACCG
MBNL1	C TTG GTG CAA CTG AAA ACA T
MBNL1	G TAA CCA ACA TTG GTG CAG T
MBNL1	T GCC CAA TAC CAG GTC AAC C
TUBB6	G CTG ACA ACG CCC ACC TAC G
TUBB6	C AGC TGG TGC ACC GAC AGT G
TUBB6	C CAT GGC CGC TAC CTG ACC G
TUBB6	C TGG CCC GGG AAG CGC AGC G
TUBB6	GTTGCAGGCCAGACGGGTGC
DDX21	C CTA CAT TCA TCG ATC CGG G
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DDX21	C ATC ACA AAA AAG CTG TCA G
DDX21	CTAGTTTGCCATTCTGTATG
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MYC	TGCGTAGTTGTGCTGATGTG
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HOXA7	GGAGCAAAGGAGCAAGAAGT
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MEIS1	ATGCGGGTCCCCATACATCG
MEIS1	CACAGCTCATACCAACGCCA
MEIS1	ATCATGATCTCTGTTCCAAG
MEIS1	CTTTAAAGCGTCATTGACAG
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CoA5	CGGCGCGTGCGCGGGCCTGA
RPL11	TGTCCACTGCACAGTTCGAG
RPL11	GGATGCGAAGTTCCCGCATG
RPL11	CTCACCTTTGGAAAACACAG
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RPL11	TTCATTTCTCCGGATGCCAA
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SRSF2	CGGGTGCAAATGGCGCGCTA
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RPS27	TTCCTCCAGGATGTTCCTTC
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HEATR1	ACAACAAAGGAACTTTACGC
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STAT5A_2	TACACCCACCTGGAGCTGCG
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BCL-2	TGTCGCAGAGGGGCTACGAG
BCL-2	CTGACGCCCTTCACCGCGCG
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NT3	ATCGTTTCCGCTTAACGGCG
NT4	GTAGGCGCGCCGCTCTCTAC
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NT7	TCATCTTACATCTGGGAGAC
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NT12	CTTACAATCGTCGGTCCAAT
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NT15	CGAGTGTTATACGCACCGTT
NT16	CGACTAACCGGAAACTTTTT
NT17	CAAGTTTTCTGAAAGGCAAT
NT18	AAAGATATAGCAAATTATGG
NT19	TTCACGTCGTCTCGCGACCA
NT20	GTGTCGGATTCCGCCGCTTA
NT21	GTTAGGAATAAAAGCTTTGA
NT22	ACTTCCCACTTCTTAGGTTG
NT23	CCATTCACAATCCCACTACA
NT24	TGTTTTGCATGTTGCATAGG
NT25	TAAGCCTCATGAAGGAGGGG
NT26	GGTACTGGAAGTCCGAAACC
NT27	AAATAATATGCATCTCTCGA
NT28	AGCTGGACTCTGTAGAAATC

Table S1. Short guide RNA (sgRNA) sequences.

Genes	Primer Sequence
USO1-Forward Primer	TACCGCTTGGAAGTGGGTAT
USO1-Reverse Primer	AAATCTTCACTCTGTCTTGTGGAAT
EPRS- Forward Primer	GGG AAG GCT TAT GTG GAT GA
EPRS- Reverse Primer	CTC GCA AAC AAC AGG ACT
EIF3E-Forward Primer	CCCTCACCTCCTTTACAGAG
EIF3E-Reverse Primer	GCACAGACTCCCTTTTCTTT
MRSP12-Forward Primer	CCTCTTCCATCAGGACCACT
MRSP12-Reverse Primer	CAGTGTCTTGTCCCAGCAG
TRFC-Forward Primer	TGGACAGCACAGACTTCACC
TRFC-Reverse Primer	CCAGGATTCTCCACCAGG
NOP16-Forward Primer	AGGGTGTAAGGCAAGGAGGT
NOP16-Reverse Primer	ATCACCCACCCTGAAAACA
DDX21-Forward Primer	GCAGCAGTTATTGGGGATGT
DDX21-Reverse Primer	TGAATTCTGGGACAGCTCCT
PSMD1-Forward Primer	CTGTGGTTGGCGTCCTTGTAT
PSMD1-Reverse Primer	CAAATGTGGATGGTTTACAG
Human 18s Forward Primer	GTAACCCGTTGAACCCCATT
Human 18s Reverse Primer	CCATCCAATCGGTAGTAGCG
Uso1-Forward Primer	CCAGGGAAGCAAAATACAGA
Uso1-Reverse Primer	GCACATAAGCCTTGGACC
L-32 Forward Primer	AAG CGA AAC TGG CGG AAA C
L-32 Reverse Primer	TAA CCG ATG TTG GGC ATC AG

Genes	ChIP primer sequence
USO1-Fw	TGGCTGAACGGCAAGATGAAT
USO1- Rev	CTGGGATTTCAGGAGCGGA

Genes	sgRNA sequence
Ms-NT	GCGAGGTATTCGGCTCCGCG
Uso1-1	GGTAACGTAGAGGAAGCTACG
Uso1-2	GTCGGTCATCCAGTAACGTAG
Uso1-3	GACTGCTGGACATTATTACAG

CRISPR Lib. primers	Sequence
Part I Illumina Universal Adaptor with variable region and vector seq.	ACACTCTTTCCCTACACGACGCTCTTCCGATCTT AA TGGAAAGGACGAAACACCGA
PartII Illumina Index adaptor	GACTGGAGTTCAGACGTGTGCTCTTCCGATCTT TTAGTTTGTATGTCTGTTG
Rest Illumina universal adaptor	AATGATACGGCGACCACCGAGATCTACACTCTT TCCCTACACGACGC
Rest Illumina Index adaptor	CAAGCAGAAGACGGCATACGAGATCGTGATGT GACTGGAGTTCAGACGTGTGC

Table S2. Primer sequences. Please see text for details.