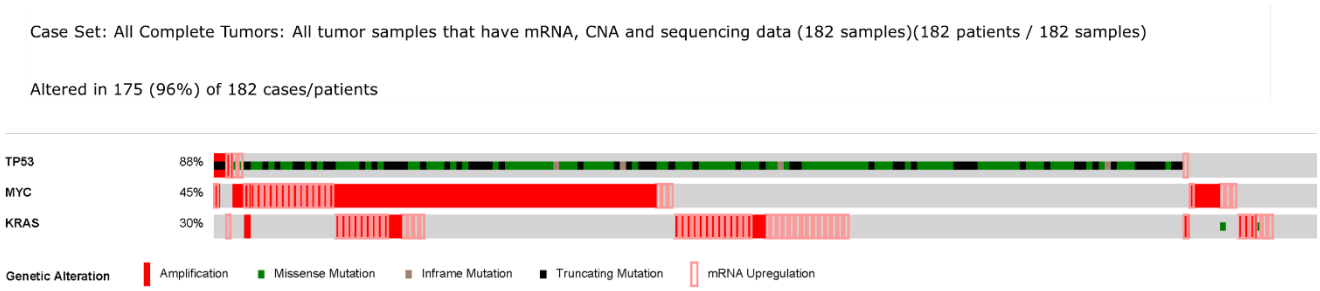
Supplementary Figures

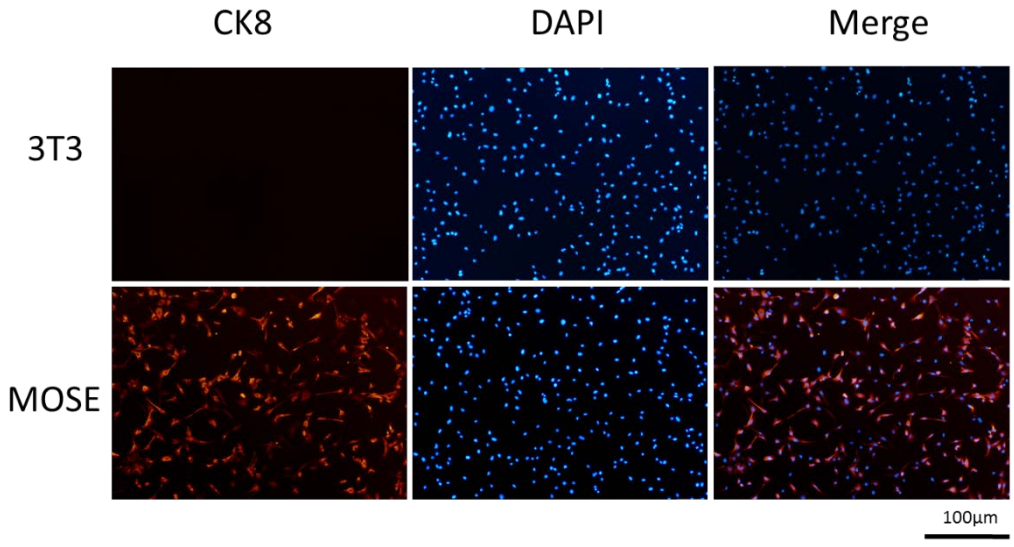
Supplementary Fig. 1



Supplementary Fig. 1 The genetic status of the KRAS, MYC and TP53 genes in ovarian cancer.

TP53, MYC and KRAS are the most frequently altered genes in ovarian serous cystadenocarcinoma. The data shown were obtained from the cBioPortal website.

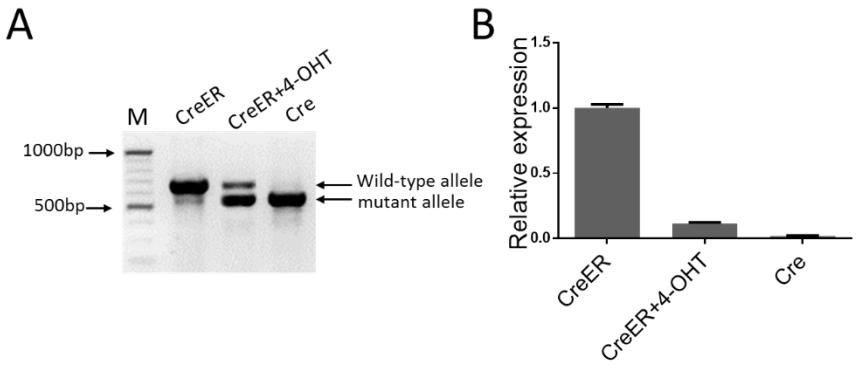
Supplementary Fig. 2



Supplementary Fig. 2 CK8 staining in cultured mouse ovarian surface epithelial cells.

The purity of isolated MOSE cells was confirmed using CK8 staining, and 3T3 cells were used as the control.

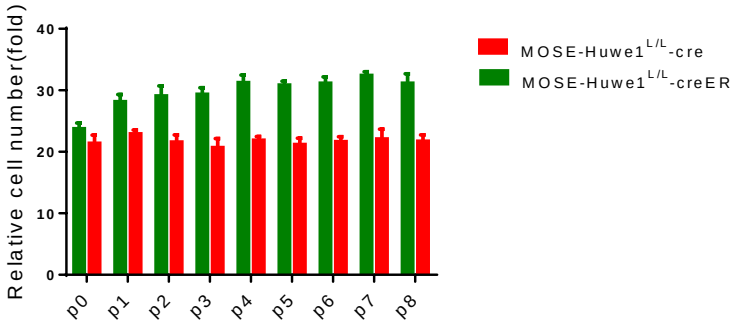
Supplementary Fig. 3



Supplementary Fig. 3 Detection of *Huwe1* knockout in MOSE cells.

(A) Genotyping PCR showing that *Huwe1* was deleted by Cre or treatment with 4-OHT in CreER-expressing cells. (B) Quantitative RT-PCR analysis of *Huwe1* mRNA expression. The results are presented as the mean ± SD.

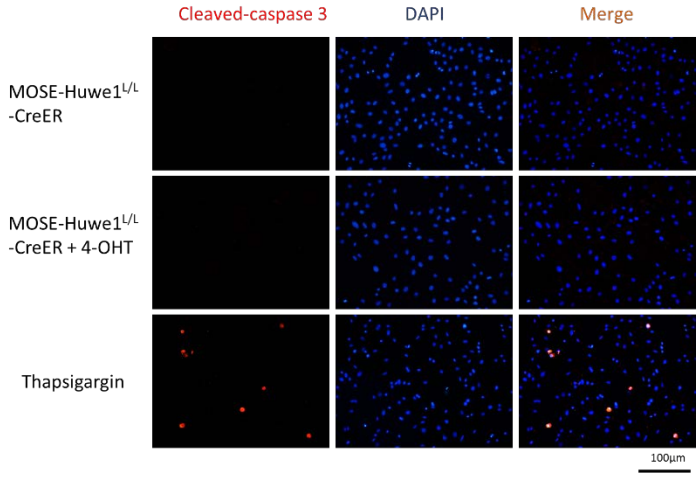
Supplementary Fig. 4



Supplementary Fig. 4 *Huwe1* knockout inhibits cell proliferation.

Relative cell numbers at different passages of MOSE-Huwe1$^{L/L}$-CreER and MOSE-Huwe$^{L/L}$-Cre cells. A total of 4*10^4 cells were seeded in 12-well plates and harvested for cell counting 60 h later. The fold-change in cell numbers relative to the number of inoculated cells is shown. The results are presented as the mean ± SD.

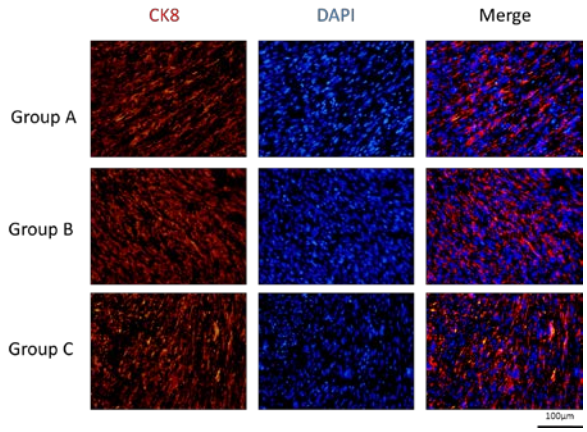
Supplementary Fig. 5



Supplementary Fig. 5 Deleting Huwe1 does not promote apoptosis in MOSE-Huwe1$^{L/L}$-CreER cells.

Cleaved-caspase 3 (red) and DAPI (blue) staining in MOSE-Huwe1$^{L/L}$-CreER and MOSE-Huwe1$^{L/L}$-CreER cells treated with 4-OHT. Thapsigargin was used to induce apoptosis in the positive control.

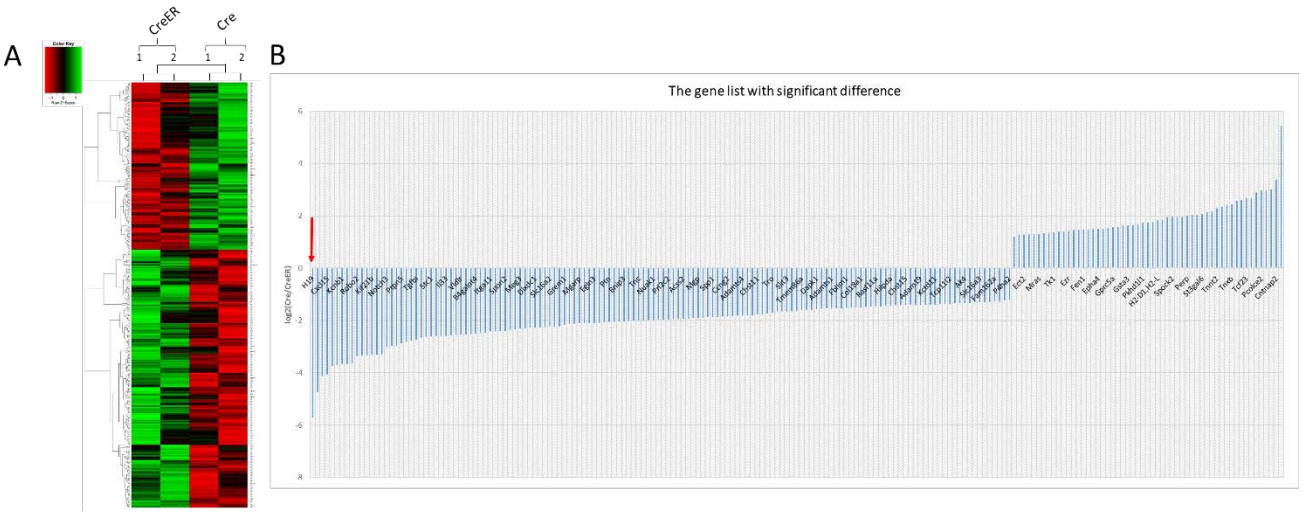
Supplementary Fig. 6



Supplementary Fig. 6 CK8 staining in tumors formed by MOSE-Huwe1$^{L/L}$-CreER cells.

CK8 (red) and DAPI (blue) staining of paraffin sections cut from the tumors generated by MOSE-Huwe1$^{L/L}$-CreER cells in BALB/c nude mice, as described in Fig. 2.

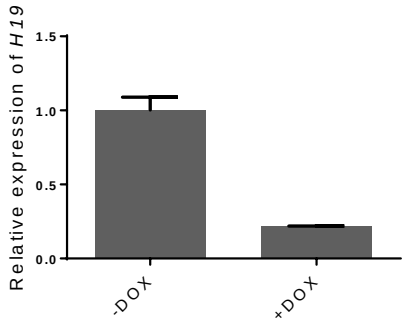
Supplementary Fig. 7



Supplementary Fig. 7 RNAseq analysis of MOSE-Huwe1$^{L/L}$-CreER and MOSE-Huwe1$^{L/L}$-Cre cells.

(A) Comparison of global changes in gene expression in MOSE-Huwe1$^{L/L}$-CreER and MOSE-Huwe1$^{L/L}$-Cre cells. Genes found to exhibit significant differences (q value ≤ 0.05 and fold-change ≥ 2) were selected for heatmap analysis in R (R Development Core Team, 2008). (B) The fold-changes observed in genes that were significantly differentially expressed. H19 was the most down-regulated gene in MOSE-Huwe1$^{L/L}$-Cre cells.

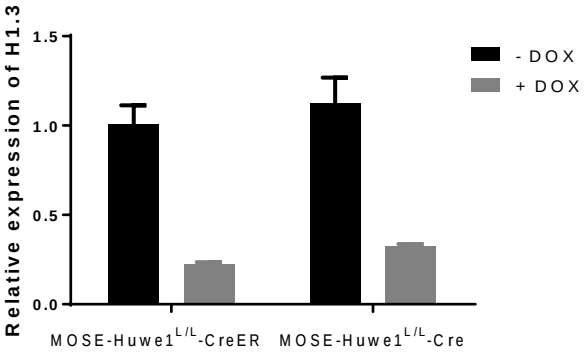
Supplementary Fig. 8



Supplementary Fig. 8 The knockdown efficiency of the *H19* shRNA in MOSE-Huwe1$^{L/L}$-CreER cells.

MOSE-Huwe1$^{L/L}$-CreER cells were infected with teton-shH19 and then treated with doxycycline for 5 days. Quantitative RT-PCR was used to determine *H19* expression levels. The results are presented as the mean ± SD

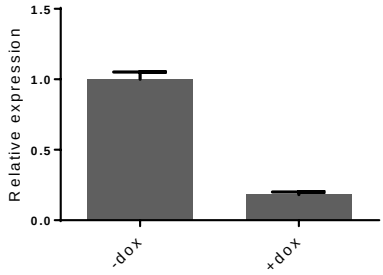
Supplementary Fig. 9



Supplementary Fig. 9 The knockdown efficiency of the *H1.3* shRNA in MOSE-Huwe1$^{L/L}$-CreER and MOSE-Huwe1$^{L/L}$-Cre cells.

MOSE-Huwe1$^{L/L}$-CreER and MOSE-Huwe1$^{L/L}$-Cre cells were infected with the teton-shH1.3 lentivirus and then treated with doxycycline for 5 days. Quantitative RT-PCR analysis showing the efficiency of H1.3 knockdown in the indicated cells. The data are presented as the means ± SD.

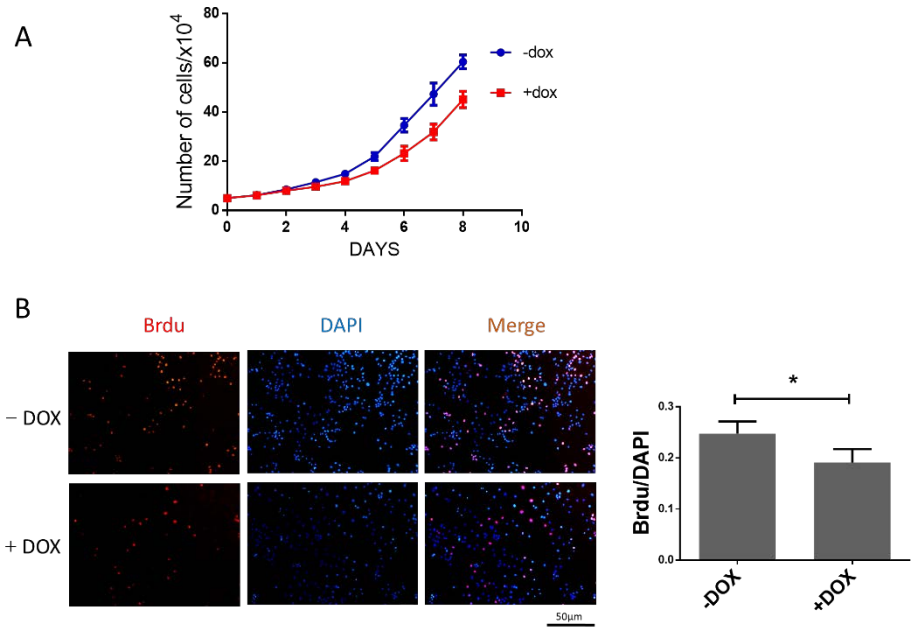
Supplementary Fig. 10



Supplementary Fig. 10 The knockdown efficiency of *HUWE1* shRNA in SKOV-3 cells.

SKOV-3 cells were infected with a teton-shHUWE1 lentivirus and then treated with doxycycline for 5 days. Quantitative RT-PCR analysis showing the efficiency of HUWE1 knockdown in SKOV-3 cells. The data are presented as the means ± SD.

Supplementary Fig. 11

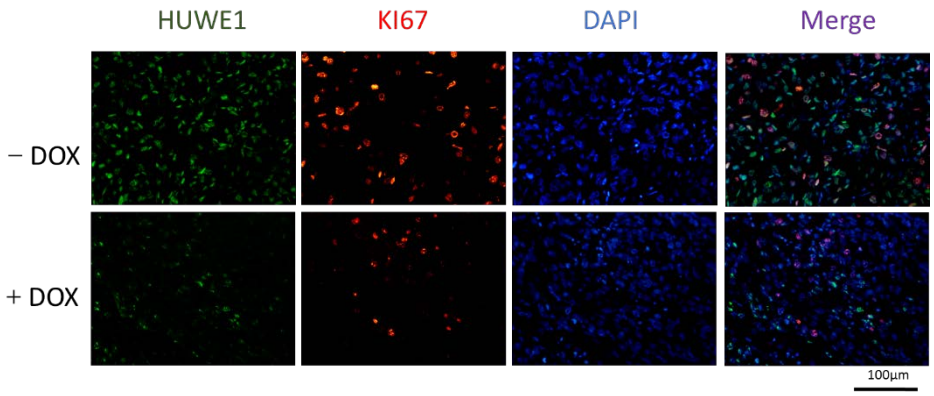


Supplementary Fig. 11 Reduced HUWE1 expression inhibited proliferation in SKOV-3 cells.

(A) Growth curves for SKOV-3/teton-shHUWE1 cells in response to DOX. The data are presented as the means ± SD. $P<0.05$ for the indicated cells. (B) A BrdU incorporation assay was used to evaluate

the rates of DNA synthesis and proliferation in SKOV-3/teton-shHUWE1 cells treated with DOX. A quantitative analysis was performed by counting the proportion of BrdU-positive cells in 7 random microscopic fields in each sample. The data are presented as the means ± SD, * P<0.05.

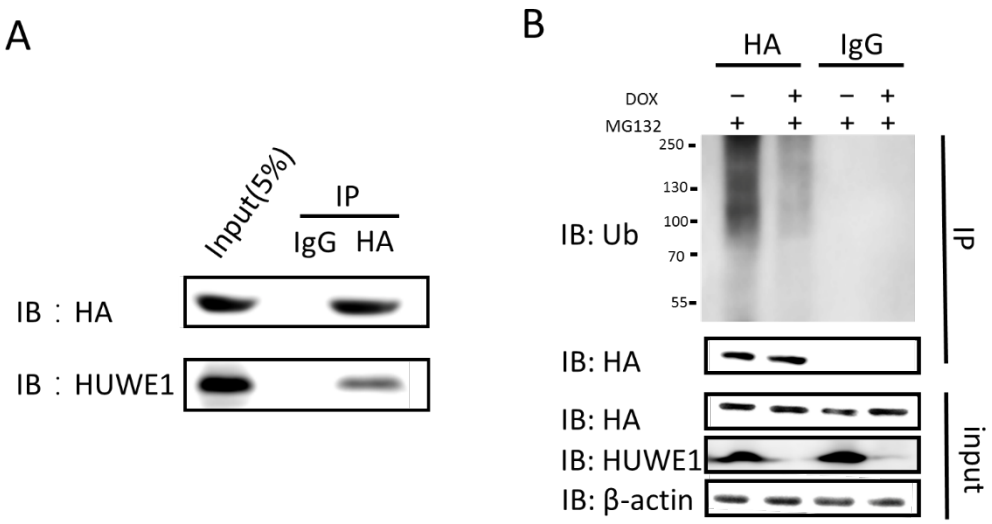
Supplementary Fig. 12



Supplementary Fig. 12 Staining for Ki67 and HUWE1 in tumors formed by SKOV-3/teton-shHUWE1 cells.

HUWE1 (green), KI67 (red) and DAPI (blue) staining in paraffin sections obtained from tumors generated by SKOV-3/teton-shHUWE1 cells in BALB/c nude mice, as described in Fig. 7.

Supplementary Fig. 13



Supplementary Fig. 13 HUWE1 binds to and ubiquitinates H1.3 in SKOV-3 cells.

(A) An interaction between HUWE1 and histone H1.3 was confirmed using co-immunoprecipitation assays in SKOV-3/teton-shHUWE1/HA-H1.3 cells. (B) Ubiquitination assays for histone H1.3. HUWE1 was knocked down by DOX in SKOV-3/teton-shHUWE1/HA-H1.3 cells. The cells were treated with 5 μM MG-132 for 6 h.