Figure S4

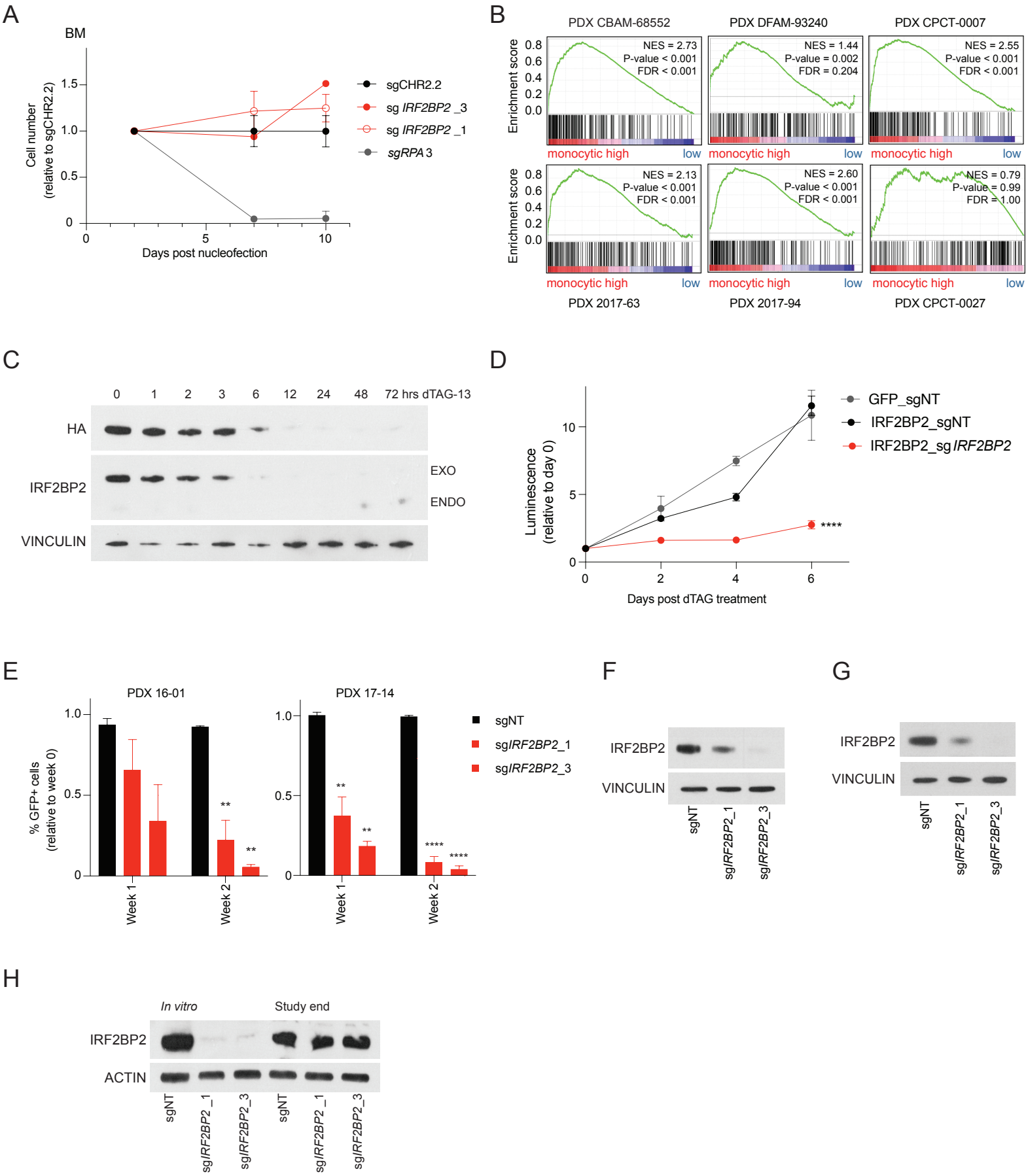
A
BM
Cell number (relative to sgCHR2.2)
Days post nucleofection
sgCHR2.2
sg IRF2BP2 _3
sg IRF2BP2 _1
sgRPA 3
B
PDX CBAM-68552
PDX DFAM-93240
PDX CPCT-0007
NES = 2.73
P-value < 0.001
FDR < 0.001
NES = 1.44
P-value = 0.002
FDR = 0.204
NES = 2.55
P-value < 0.001
FDR < 0.001
NES = 2.13
P-value < 0.001
FDR < 0.001
NES = 2.60
P-value < 0.001
FDR < 0.001
NES = 0.79
P-value = 0.99
FDR = 1.00
Enrichment score
monocytic high
low
PDX 2017-63
PDX 2017-94
PDX CPCT-0027
C
0 1 2 3 6 12 24 48 72 hrs dTAG-13
HA
IRF2BP2
EXO
ENDO
VINCULIN
D
Luminescence (relative to day 0)
Days post dTAG treatment
GFP_sgNT
IRF2BP2_sgNT
IRF2BP2_sg IRF2BP2
****
E
PDX 16-01
PDX 17-14
% GFP+ cells (relative to week 0)
sgNT
sgIRF2BP2_1
sgIRF2BP2_3
Week 1
Week 2
F
IRF2BP2
VINCULIN
sgNT
sgIRF2BP2_1
sgIRF2BP2_3
G
IRF2BP2
VINCULIN
sgNT
sgIRF2BP2_1
sgIRF2BP2_3
H
In vitro
Study end
IRF2BP2
ACTIN
sgNT
sgIRF2BP2 _1
sgIRF2BP2_3

Figure S4. Knock-down of *IRF2BP2* in PDX cells reduces leukemia burden

A, Serial cell counting of hCD34+ bone marrow cells nucleofected with synthetic *IRF2BP2*-targeting guides, a non-targeting control guide or a positive control guide targeting an essential gene (*RPA3*).

B, GSEA for human monocytic lineage gene markers (35) run per individual PDX sample on the genome-wide genes ranked by log2(TPM+1) expression. NES >/= 1.3, p-value </= 0.05, FDR </= 0.25.

C, Western blot analysis of a time-course experiment showing IRF2BP2 protein levels following treatment with dTAG-13 in PDX 16-01 cells with a degradable N-terminally tagged $FKBP12^{F36V}$-HA-*IRF2BP2*-fusion and knock-out of endogenous *IRF2BP2*. Vinculin was used as a loading control.

D, CellTiter-Glo viability assay in PDX 16-01 cells overexpressing a GFP CTRL-ORF or an *IRF2BP2* N-dTAG-construct, double-infected with non-targeting (sgNT) or CRISPR guide targeting endogenous *IRF2BP2* (sg*IRF2BP2*) following treatment with 500 nM dTAG-13. Two-way ANOVA, **** $p < 0.0001$.

E, Flow cytometry for GFP in PDX16-01 (left) and PDX17-14 cells (right) infected with GFP-marked sgNT, or sg*IRF2BP2* on the day of doxycycline-induction and at one and two weeks. One-way ANOVA, Dunnett's multiple comparison test (per week), ** $p < 0.01$, **** $p < 0.0001$.

F, Western blot analysis from the model PDX 16-01 infected with doxycycline-inducible non-targeting CRISPR guides (sgNT), or CRISPR guides against *IRF2BP2* (sg*IRF2BP2*_1, sg*IRF2BP2*_3) four days after doxycycline-induction of *IRF2BP2* knock-out. Vinculin was used as a loading control.

G, Western blot analysis from the model PDX 17-14 infected with doxycycline-inducible non-targeting CRISPR guides (sgNT), or CRISPR guides against *IRF2BP2* (sg*IRF2BP2*_1, sg*IRF2BP2*_3) four days after doxycycline-induction of *IRF2BP2* knock-out. Vinculin was used as a loading control.

H, Western blot analysis from the model PDX 17-14 infected with doxycycline-inducible non-targeting CRISPR guides (sgNT), or CRISPR guides against *IRF2BP2* (sg*IRF2BP2*_1, sg*IRF2BP2*_3) in cells treated with doxycycline *in vitro* as a control for knock-out with this system and in bone marrow cells of the respective *in vivo* recipients at study end. Actin was used as a loading control.