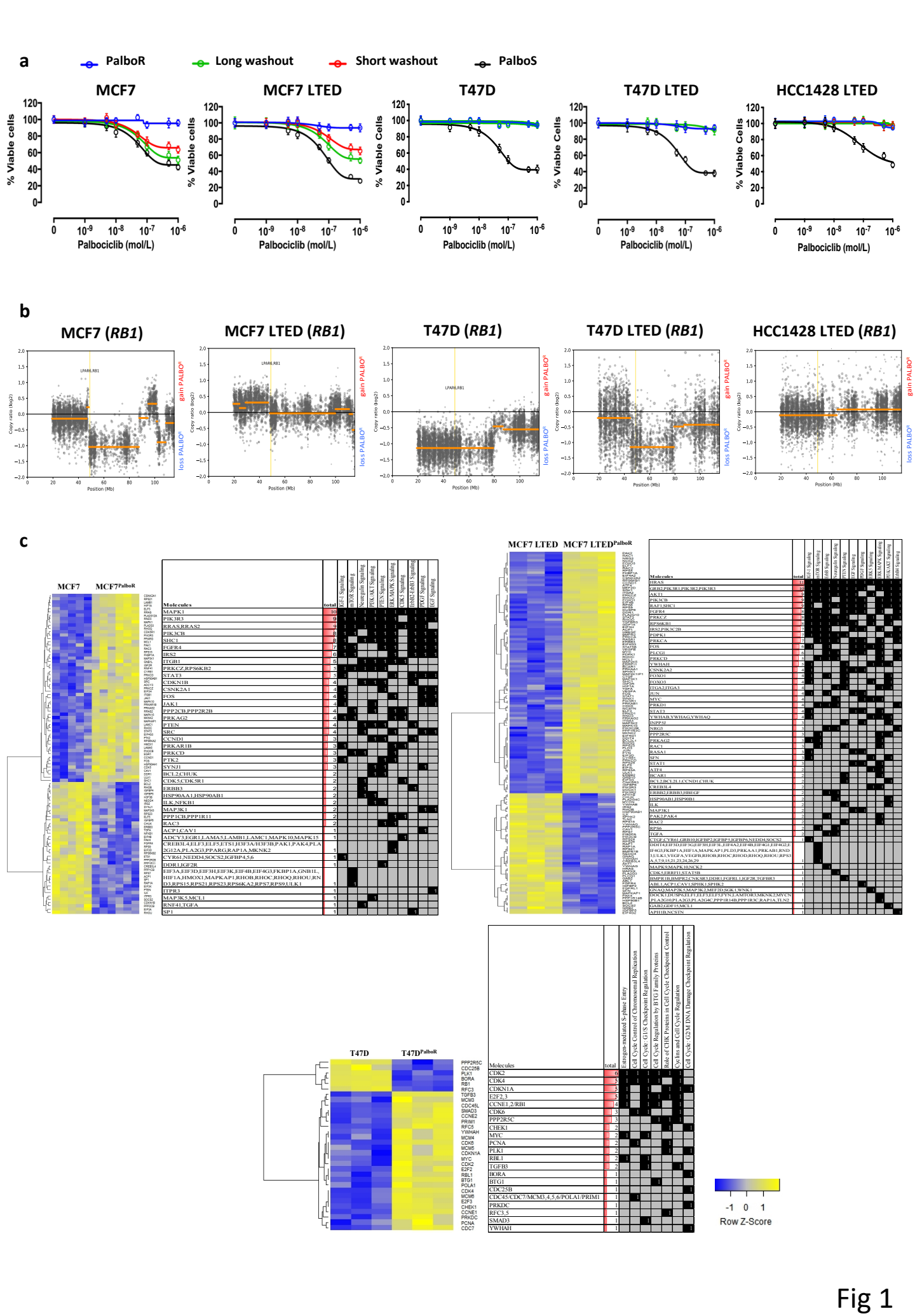
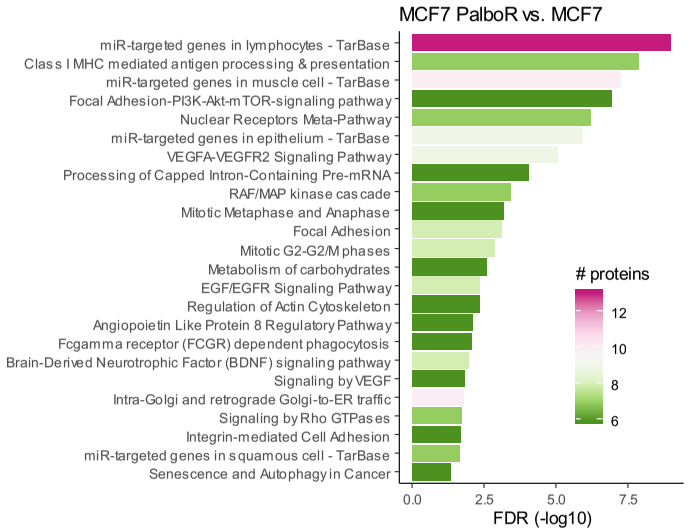
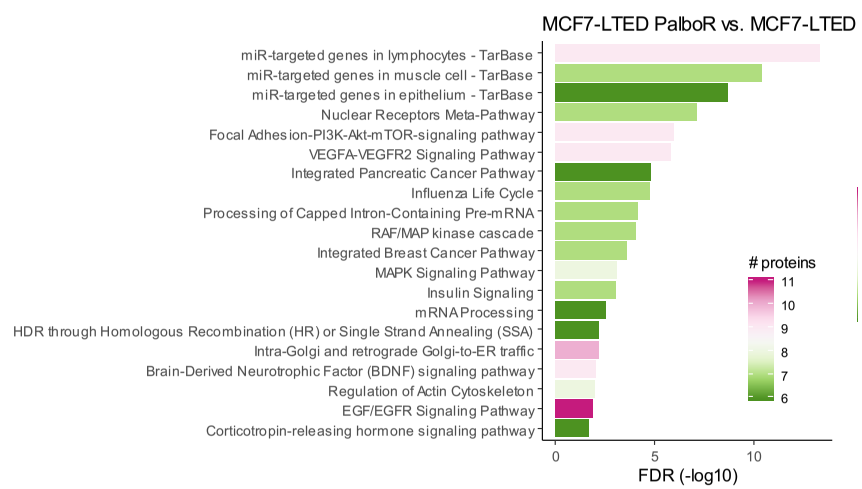
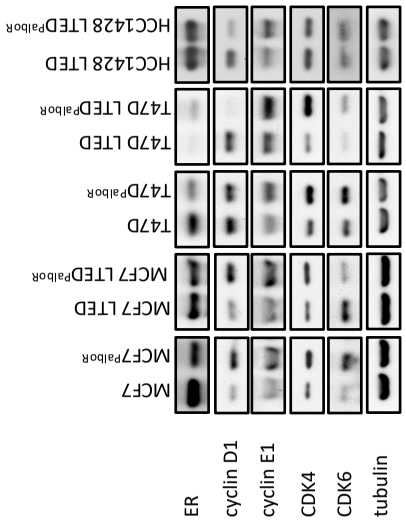

a
PalboR
Long washout
Short washout
PalboS
MCF7
MCF7 LTED
T47D
T47D LTED
HCC1428 LTED
% Viable cells
Palbociclib (mol/L)
b
MCF7 (RB1)
MCF7 LTED (RB1)
T47D (RB1)
T47D LTED (RB1)
HCC1428 LTED (RB1)
gain PALBOR
loss PALBOR
Copy ratio (log2)
Position (Mb)
c
MCF7
MCF7PalboR
MCF7 LTED
MCF7 LTEDPalboR
T47D
T47DPalboR
Molecules
total
Row Z-Score

Fig 1

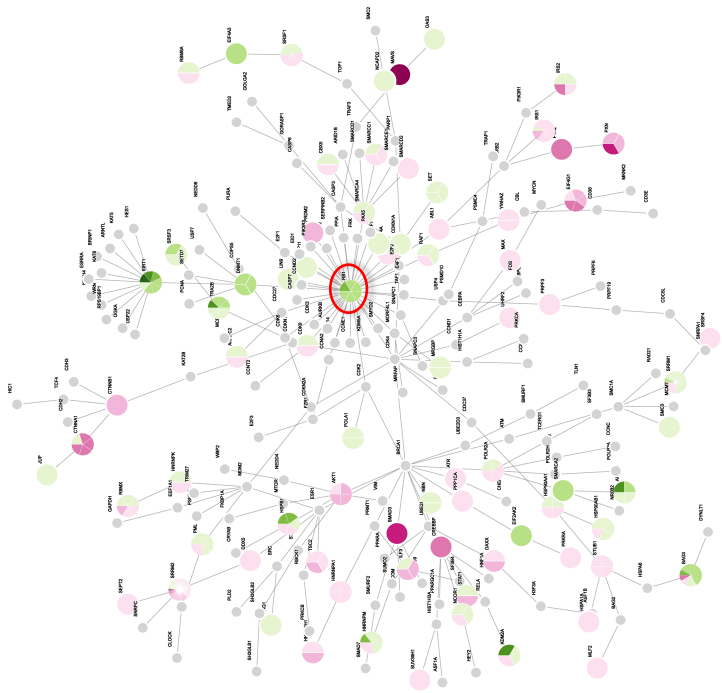
Fig 2





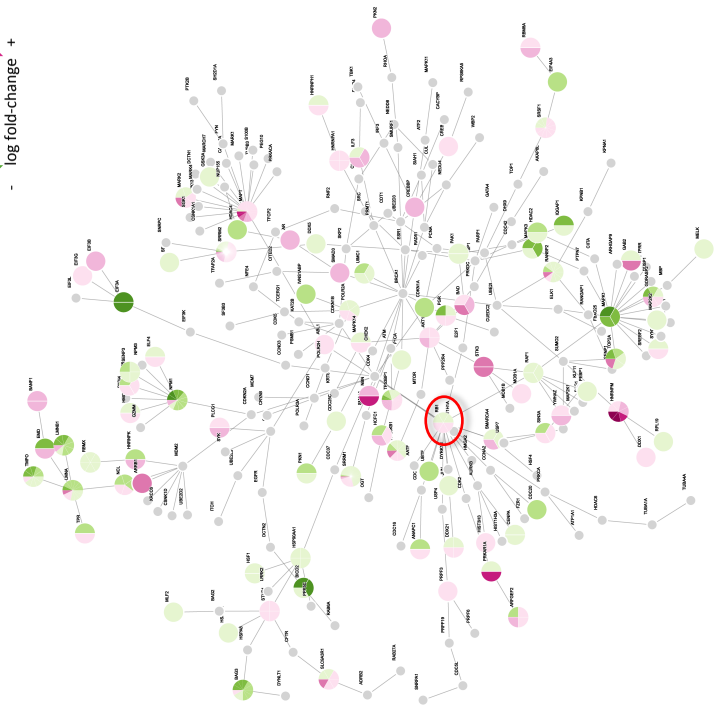


a



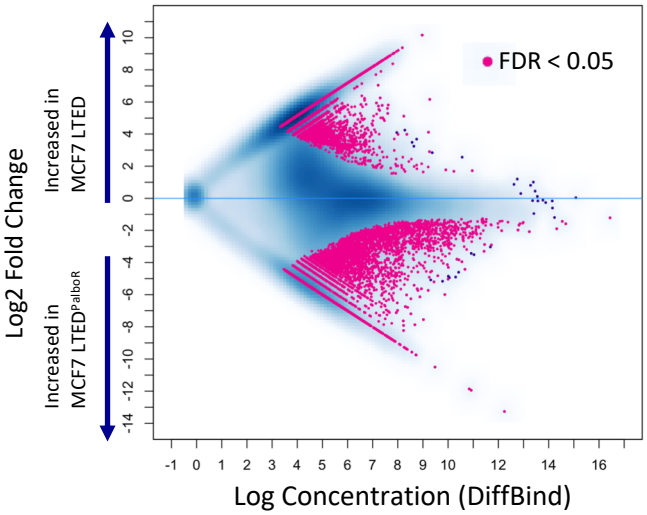
b

MCF7$_{PalboR}$ vs. MCF7

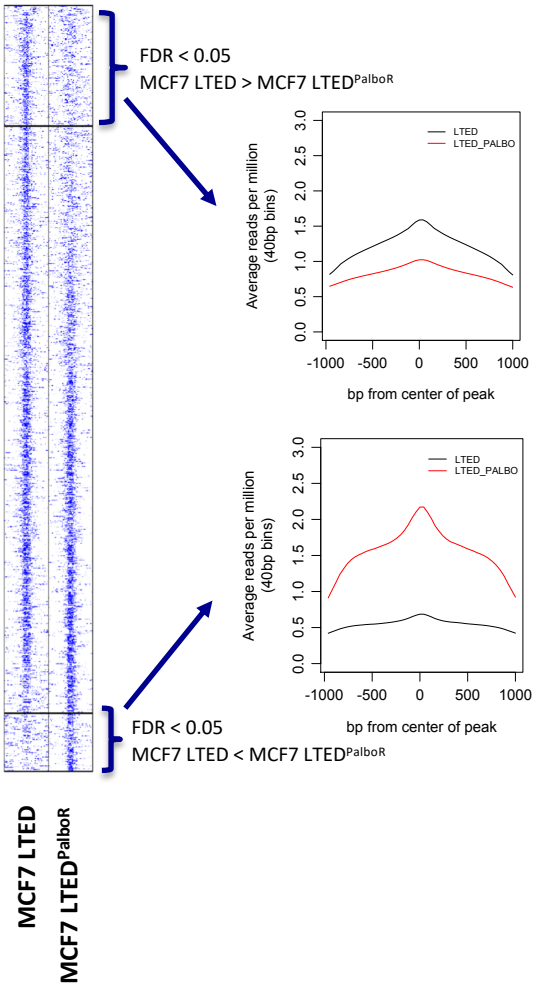


MCF7 LTED$_{PalboR}$ vs. MCF7 LTED

a



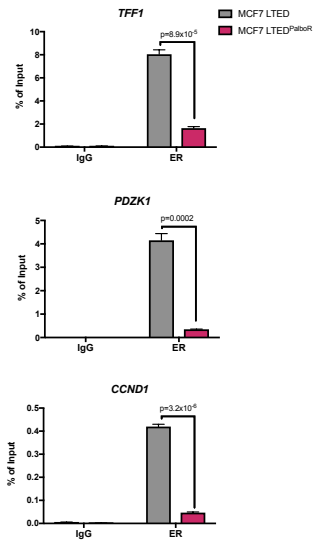
b



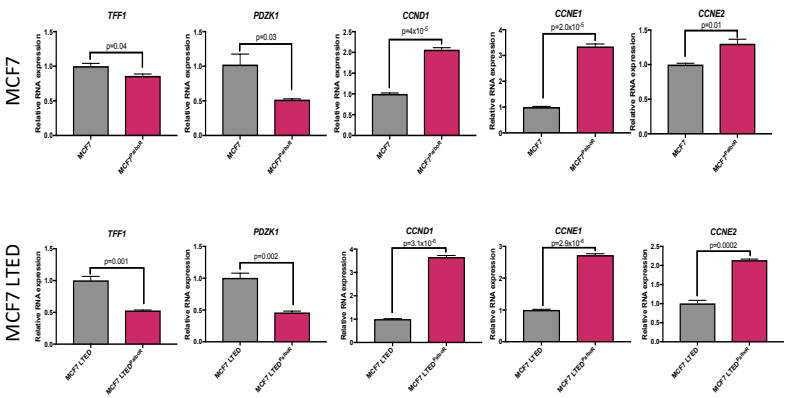
c

Motif (HOCOMOCO v11)	Consensus Motif	Adj. p value (MCF7 LTED > MCF7 LTED^{PalboR})	Adj. p value (MCF7 LTED < MCF7 LTED^{PalboR})
AP2B		1.80×10^{-35}	2.50×10^{-75}
CREB1		1.10×10^{-24}	1
E2F4		2.60×10^{-6}	1.20×10^{-44}
E2F7		1	8.30×10^{-40}
ESR1		9.20×10^{-302}	2.20×10^{-35}
FOXA1		2.3×10^{-45}	1
SP1		0.14	1.40×10^{-11}

d



e



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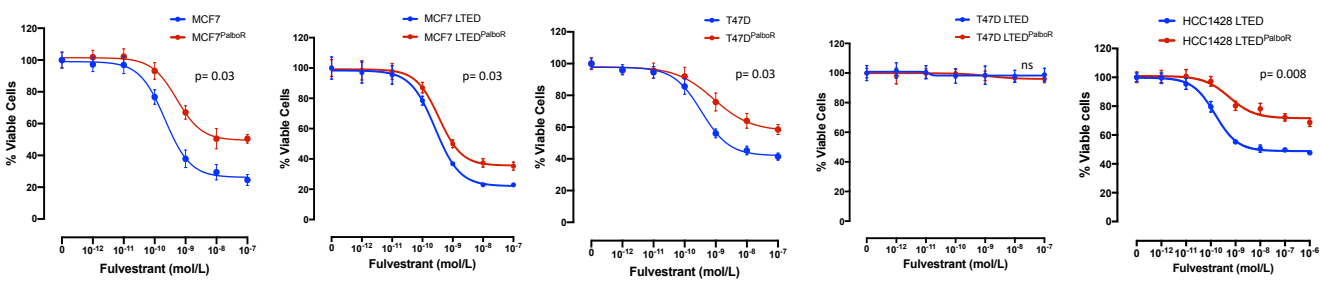


Fig 3

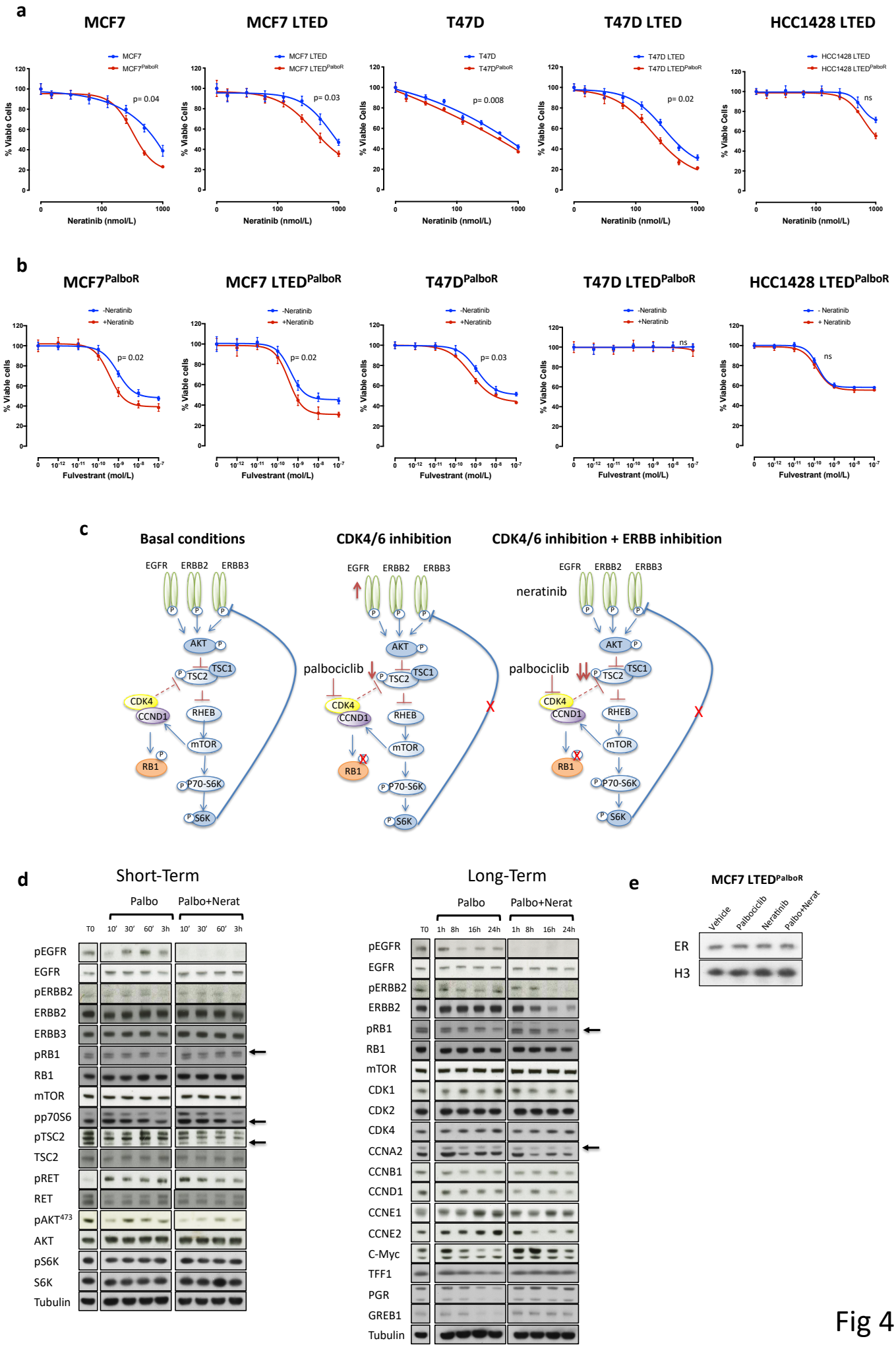
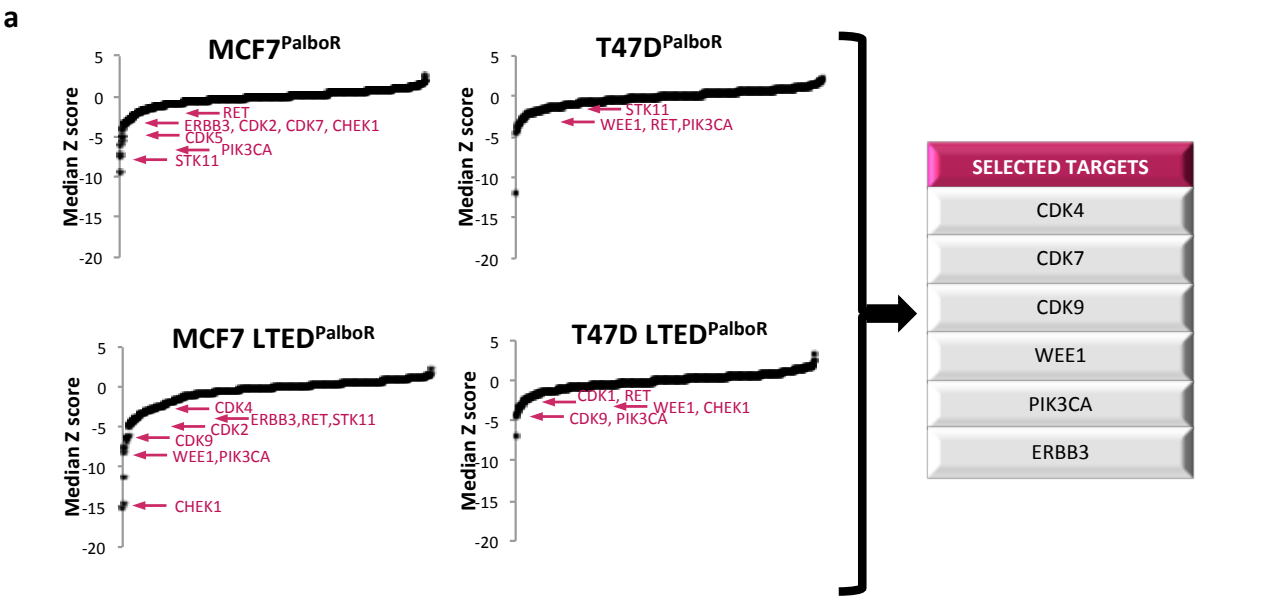

a
MCF7
MCF7 LTED
T47D
T47D LTED
HCC1428 LTED
MCF7
MCF7PalboR
MCF7 LTED
MCF7 LTEDPalboR
T47D
T47DPalboR
T47D LTED
T47D LTEDPalboR
HCC1428 LTED
HCC1428 LTEDPalboR
p= 0.04
p= 0.03
p= 0.008
p= 0.02
ns
% Viable Cells
Neratinib (nmol/L)
b
MCF7PalboR
MCF7 LTEDPalboR
T47DPalboR
T47D LTEDPalboR
HCC1428 LTEDPalboR
-Neratinib
+Neratinib
p= 0.02
p= 0.02
p= 0.03
ns
ns
% Viable Cells
Fulvestrant (mol/L)
c
Basal conditions
CDK4/6 inhibition
CDK4/6 inhibition + ERBB inhibition
EGFR
ERBB2
ERBB3
neratinib
palbociclib
palbociclib
AKT
TSC1
TSC2
CDK4
CCND1
RHEB
mTOR
RB1
P70-S6K
S6K
d
Short-Term
Palbo
Palbo+Nerat
T0
10′
30′
60′
3h
pEGFR
EGFR
pERBB2
ERBB2
ERBB3
pRB1
RB1
mTOR
pp70S6
pTSC2
TSC2
pRET
RET
pAKT473
AKT
pS6K
S6K
Tubulin
Long-Term
Palbo
Palbo+Nerat
T0
1h
8h
16h
24h
pEGFR
EGFR
pERBB2
ERBB2
pRB1
RB1
mTOR
CDK1
CDK2
CDK4
CCNA2
CCNB1
CCND1
CCNE1
CCNE2
C-Myc
TFF1
PGR
GREB1
Tubulin
e
MCF7 LTEDPalboR
Vehicle
Palbociclib
Neratinib
Palbo+Nerat
ER
H3

Fig 4


a
MCF7PalboR
Median Z score
RET
ERBB3, CDK2, CDK7, CHEK1
CDK5
PIK3CA
STK11
T47DPalboR
STK11
WEE1, RET,PIK3CA
MCF7 LTEDPalboR
CDK4
ERBB3,RET,STK11
CDK2
CDK9
WEE1,PIK3CA
CHEK1
T47D LTEDPalboR
CDK1, RET
WEE1, CHEK1
CDK9, PIK3CA
SELECTED TARGETS
CDK4
CDK7
CDK9
WEE1
PIK3CA
ERBB3

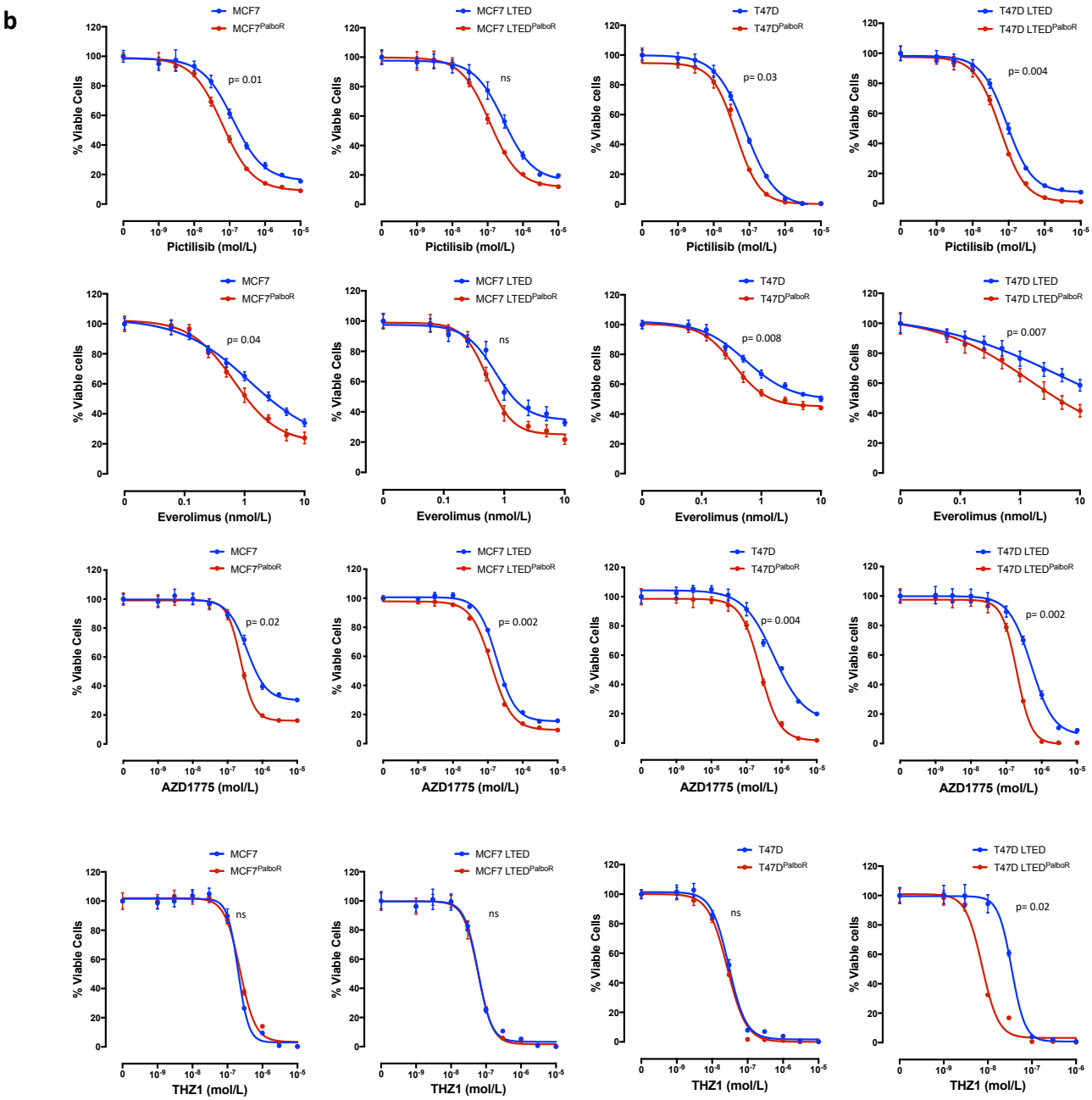
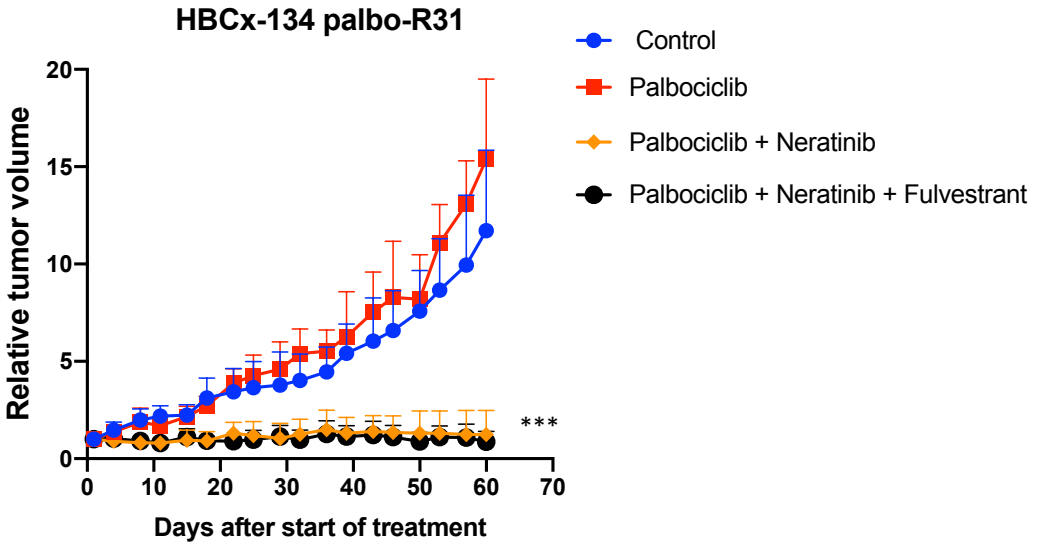
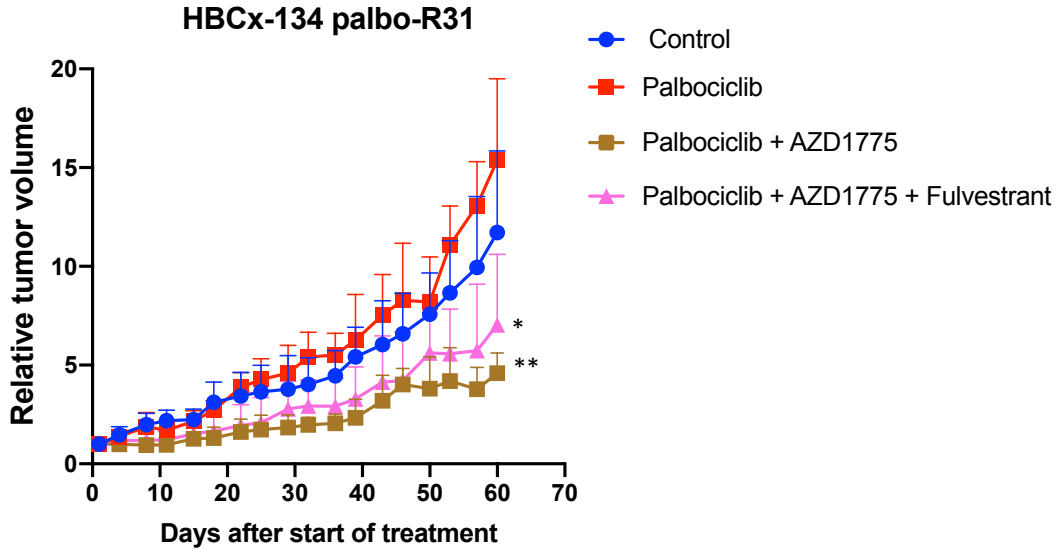

b
MCF7
MCF7PalboR
MCF7 LTED
MCF7 LTEDPalboR
T47D
T47DPalboR
T47D LTED
T47D LTEDPalboR
% Viable Cells
% Viable cells
p= 0.01
ns
p= 0.03
p= 0.004
Pictilisib (mol/L)
p= 0.04
ns
p= 0.008
p= 0.007
Everolimus (nmol/L)
p= 0.02
p= 0.002
p= 0.004
p= 0.002
AZD1775 (mol/L)
ns
ns
ns
p= 0.02
THZ1 (mol/L)

Fig 5


HBCx-134 palbo-R31
Relative tumor volume
Days after start of treatment
Control
Palbociclib
Palbociclib + Neratinib
Palbociclib + Neratinib + Fulvestrant
***


HBCx-134 palbo-R31
Relative tumor volume
Days after start of treatment
Control
Palbociclib
Palbociclib + AZD1775
Palbociclib + AZD1775 + Fulvestrant
*
**

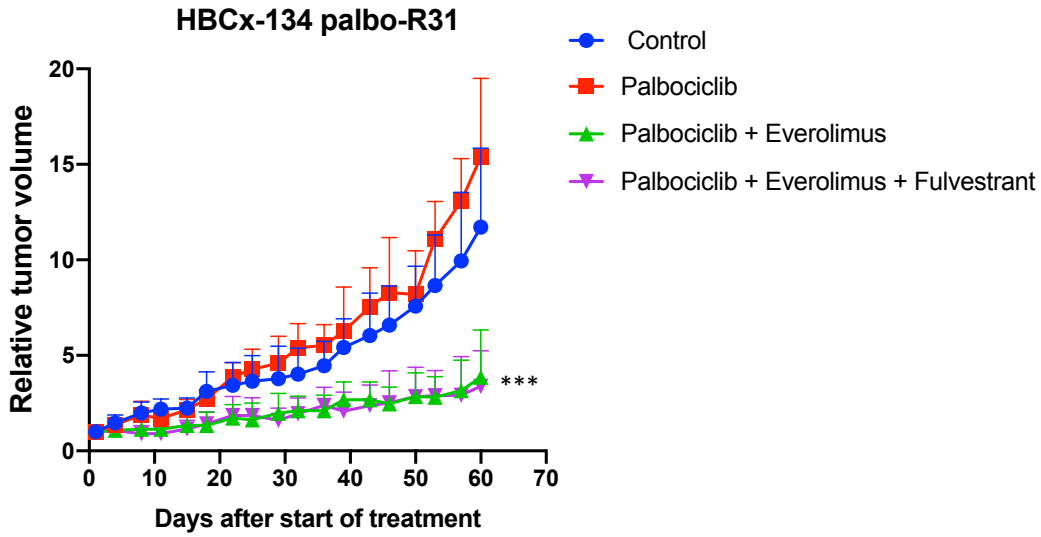

HBCx-134 palbo-R31
Relative tumor volume
Days after start of treatment
Control
Palbociclib
Palbociclib + Everolimus
Palbociclib + Everolimus + Fulvestrant
***

Fig 6

Supplementary Figure and Files Legends

Supplementary Figure S1. Effect of palbociclib alone or in combination with endocrine agents was assessed in cell line models sensitive and resistant to E-deprivation. (**a**) Effect of escalating doses of palbociclib on the proliferation of several cell line models both in the absence and in the presence of 0.01nM estradiol (E2) over a period of 6 days. Data represented in relative luminescence units (RLU) (n=2 biological replicates with n=8 technical replicates per concentration). (**b**) Antiproliferative effect of escalating doses of palbociclib in 3D spheroid models of MCF7 and MCF7 LTED. (**c**) Antiproliferative effect of palbociclib, 4-hydroxytamoxifen (4OHT) or fulvestrant (Fulv) alone or in combination (Combo). Data represents percentage (%) of viable cells compared to E2 control for each cell line. Error bars represent mean ± SEM. *p<0.05; **p<0.01; ***p<0.001. (**d**) Effect of combination of palbociclib with E-deprivation (DCC), 4OHT or Fulv on cell cycle targets and ER signalling in MCF7 LTED cell lines (n=2 biological replicates) after 24 hours treatment. E2 (0.01nM), 4OHT (10nM), Fulv (1nM), palbociclib (100nM). Arrow shows position of phosphorylated RB.

Supplementary Figure S2. (a) Assessment of expression of several cell cycle markers in MCF7 LTED treated with vehicle (0.01% v/v DMSO) or palbociclib (1uM) compared to the palbociclib-resistant LTED (MCF7 LTED^{palboR}) in the presence of palbociclib (1uM). Cells were harvested after 24 hours treatment (n=2 biological replicates). (**b**) Effect of drug holiday on response to palbociclib. Long-term study assessing changes in median tumour volumes over 127 days of treatment with palbociclib, showing earlier onset of resistance. Therapy was withdrawn for a further 6 weeks and then restarted on day 167. Statistical significance was calculated using

Wilcoxon matched pairs signed rank test. Data was available for n=9 animals per group. (**c**) Assessment of *RB1* expression in several cell line models of palbociclib-sensitive and resistance disease. Error bars represent means ± SEM. (**d**) Immunoblotting showing RB1 levels in palbociclib-sensitive, resistant and washouts experiments in MCF7, MCF7 LTED, T47D, T47D LTED and HCC1428 LTED cell lines (n=3 biological replicates).

Supplementary Figure S3 (a) Heat-map representation of cell cycle associated genes in MCF7 LTED parental versus MCF7 LTED^{PalboR} (n=3 biological replicates). (**b**) Real time live cell imaging over 144 hours for MCF7 LTED versus MCF7 LTED^{PalboR} cell lines. (**c**) Heatmap showing Oncogenic Signatures from the Molecular Signature Database at Broad Institute significant (FDR < 0.01 in any condition) in MCF7 vs. MCF7^{PalboR} and MCF7 LTED versus MCF7 LTED^{PalboR} cell lines.

Supplementary Figure S4. Assessment of expression of *EGFR*, *MAPK1*, *MAP3K1*, *CDK2*, *CDK4*, *CDK7*, *CCNE1* and *CCNE2* in several models of palbociclib-sensitive and -resistance disease. Error bars represent means ± SEM.

Supplementary Figure S5. (**a**) Assessment of *ESR1* expression in several models of palbociclib-sensitive and -resistance disease. Error bars represent means ± SEM. (**b**) Expression levels of growth factor signalling markers in palbociclib-sensitive and -resistant in MCF7 and MCF7 LTED cell lines (n=2 biological replicates).

Supplementary Figure S6. (**a**) Hallmark pathways enriched in MCF7 LTED^{PalboR} versus MCF7 LTED (by GSEA). (**b-c**) gProfiler analysis of genes involved in early and late

estrogen response that are (**b**) downregulated and (**c**) upregulated in MCF7 LTED^{PalboR} versus MCF7 LTED cell lines.

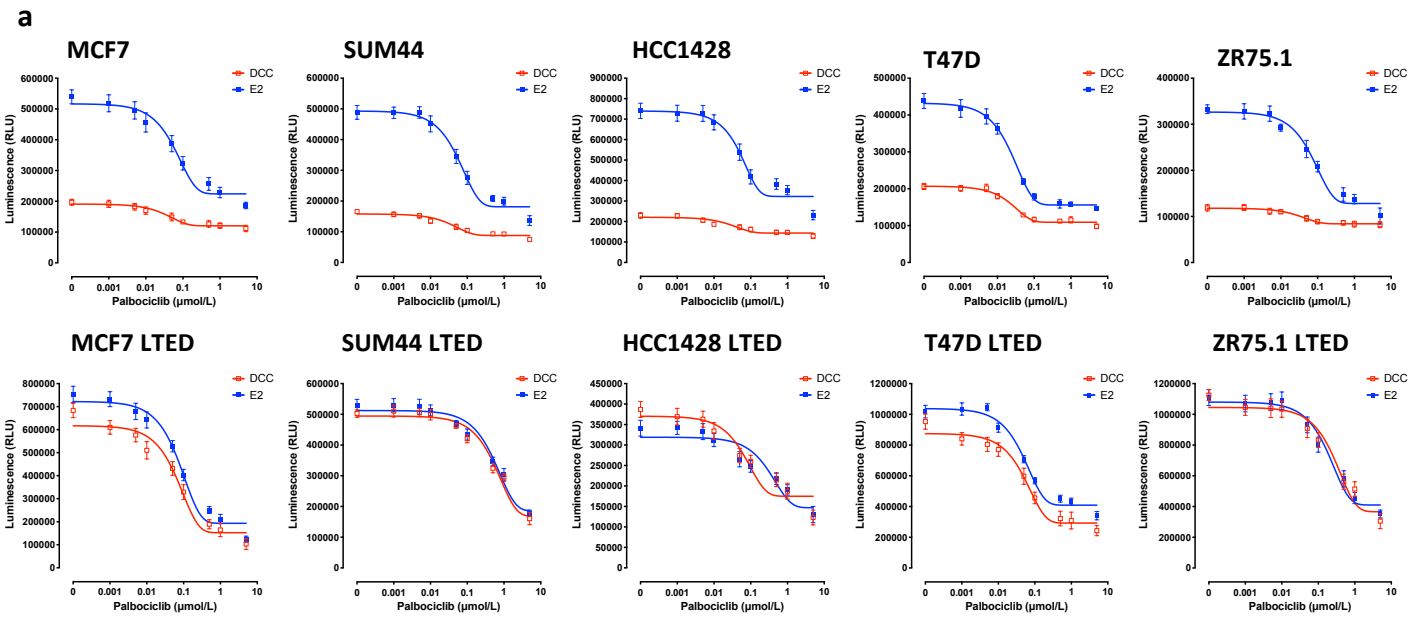
Supplementary Figure S7. Effect of escalating concentrations of **(a)** 4OHT (4-hydroxytamoxifen), **(b)** AZD8931 (EGFR/ERBB inhibitor) and (**c**) LDC000067 (CDK9 inhibitor) in MCF7^{PalboR}, MCF7 LTED^{PalboR}, T47D^{PalboR} and T47D LTED^{PalboR} versus their corresponding parental cell lines (n=3 biological and n=8 technical replicates). Data represents % viable cells compared to vehicle control for each cell line. Error bars represent mean ± SEM.

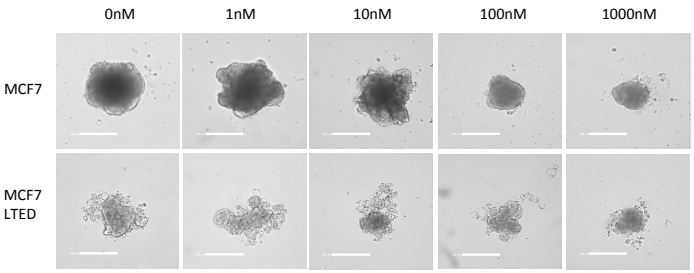
Supplementary File S1. Pathway analysis using Ingenuity Pathway Analysis (IPA) based on gene expression data.

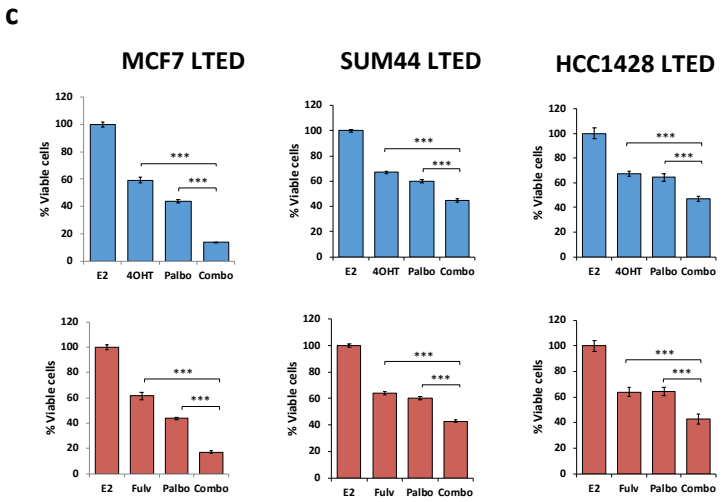
Supplementary File S2. Comparison of global phosphoproteomic and total protein changes associated with palbociclib resistance.

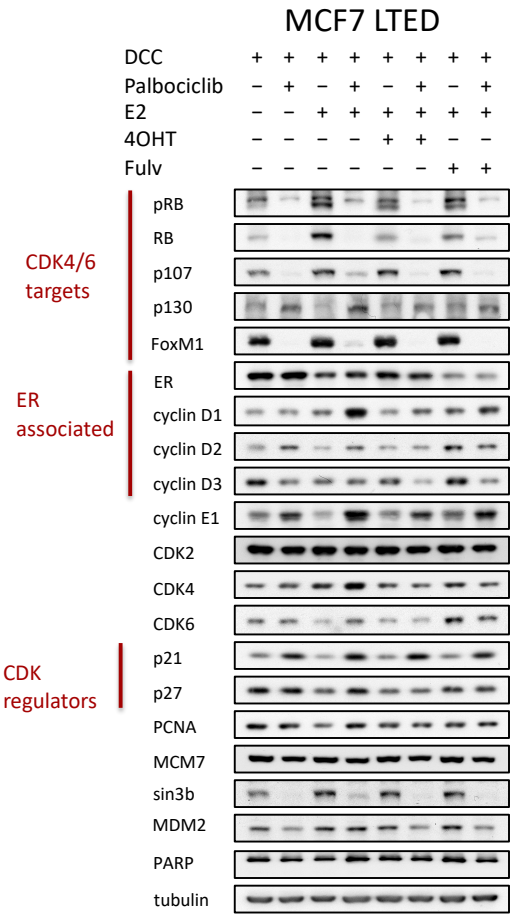
Supplementary File S3. Image J band quantification relative to tubulin controls and normalised to T0.

Supplementary File S4. List of kinases associated with resistance to CDK4/6 inhibitions.

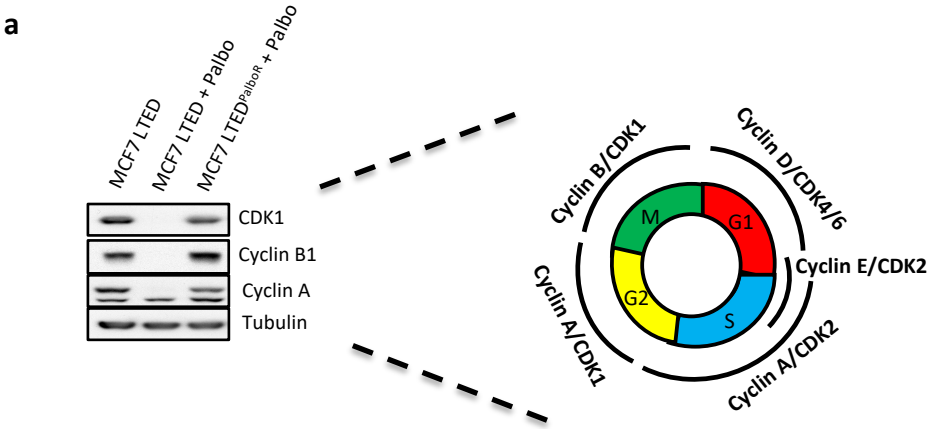

a
MCF7
SUM44
HCC1428
T47D
ZR75.1
MCF7 LTED
SUM44 LTED
HCC1428 LTED
T47D LTED
ZR75.1 LTED
DCC
E2
Luminescence (RLU)
Palbociclib (μmol/L)

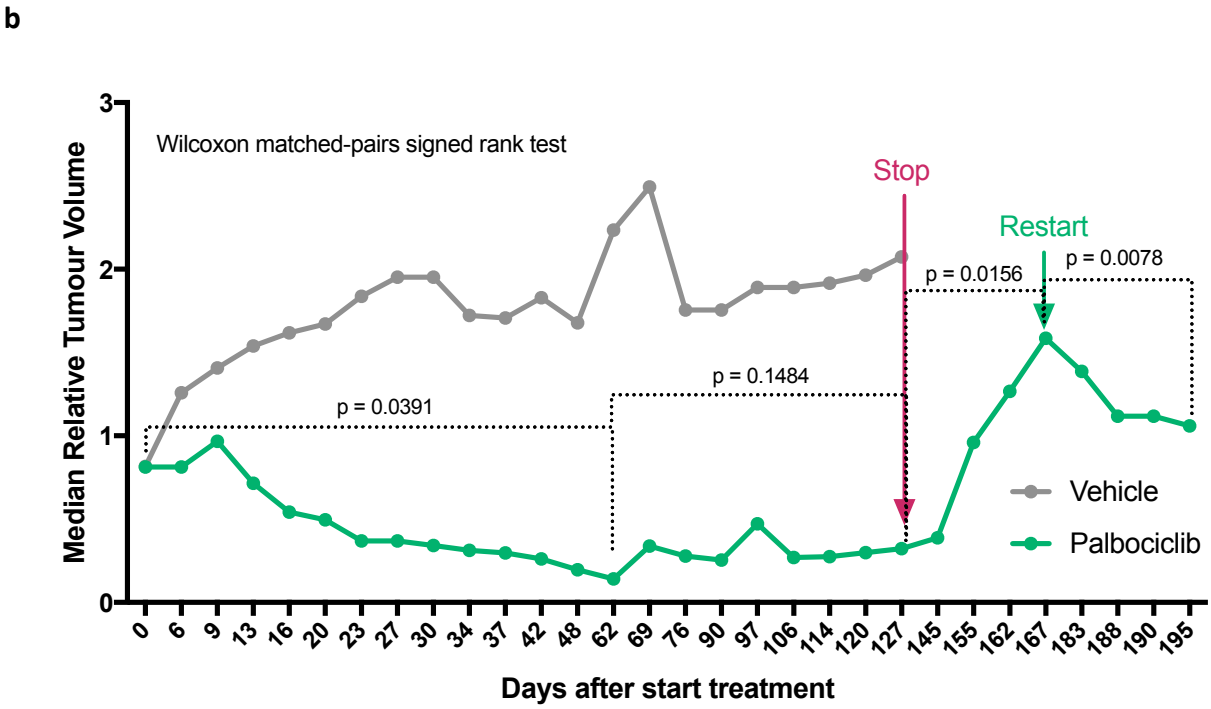

b
0nM
1nM
10nM
100nM
1000nM
MCF7
MCF7 LTED

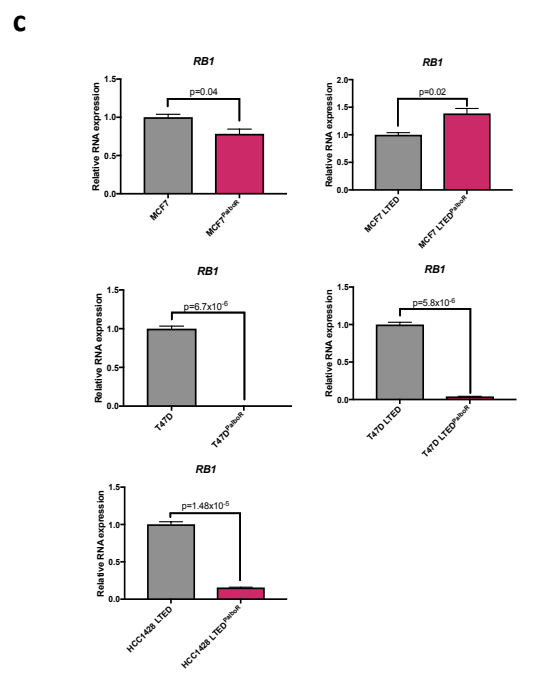

c
MCF7 LTED
SUM44 LTED
HCC1428 LTED
% Viable cells
E2
4OHT
Palbo
Combo
Fulv

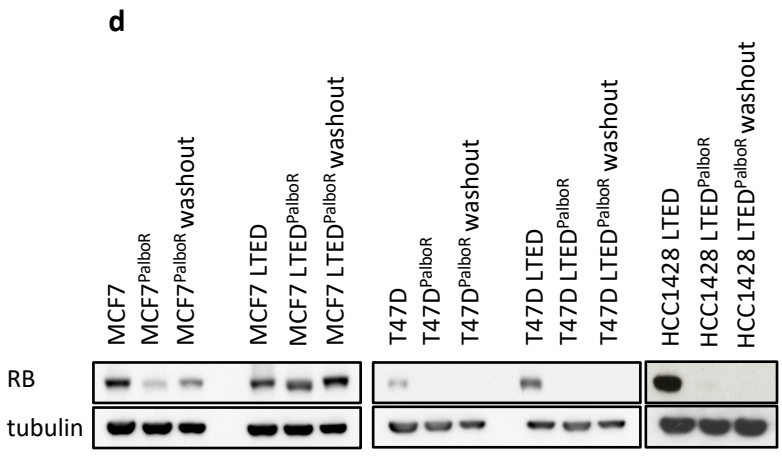

d
MCF7 LTED
DCC
Palbociclib
E2
4OHT
Fulv
CDK4/6 targets
ER associated
CDK regulators
pRB
RB
p107
p130
FoxM1
ER
cyclin D1
cyclin D2
cyclin D3
cyclin E1
CDK2
CDK4
CDK6
p21
p27
PCNA
MCM7
sin3b
MDM2
PARP
tubulin

Supp Fig S1

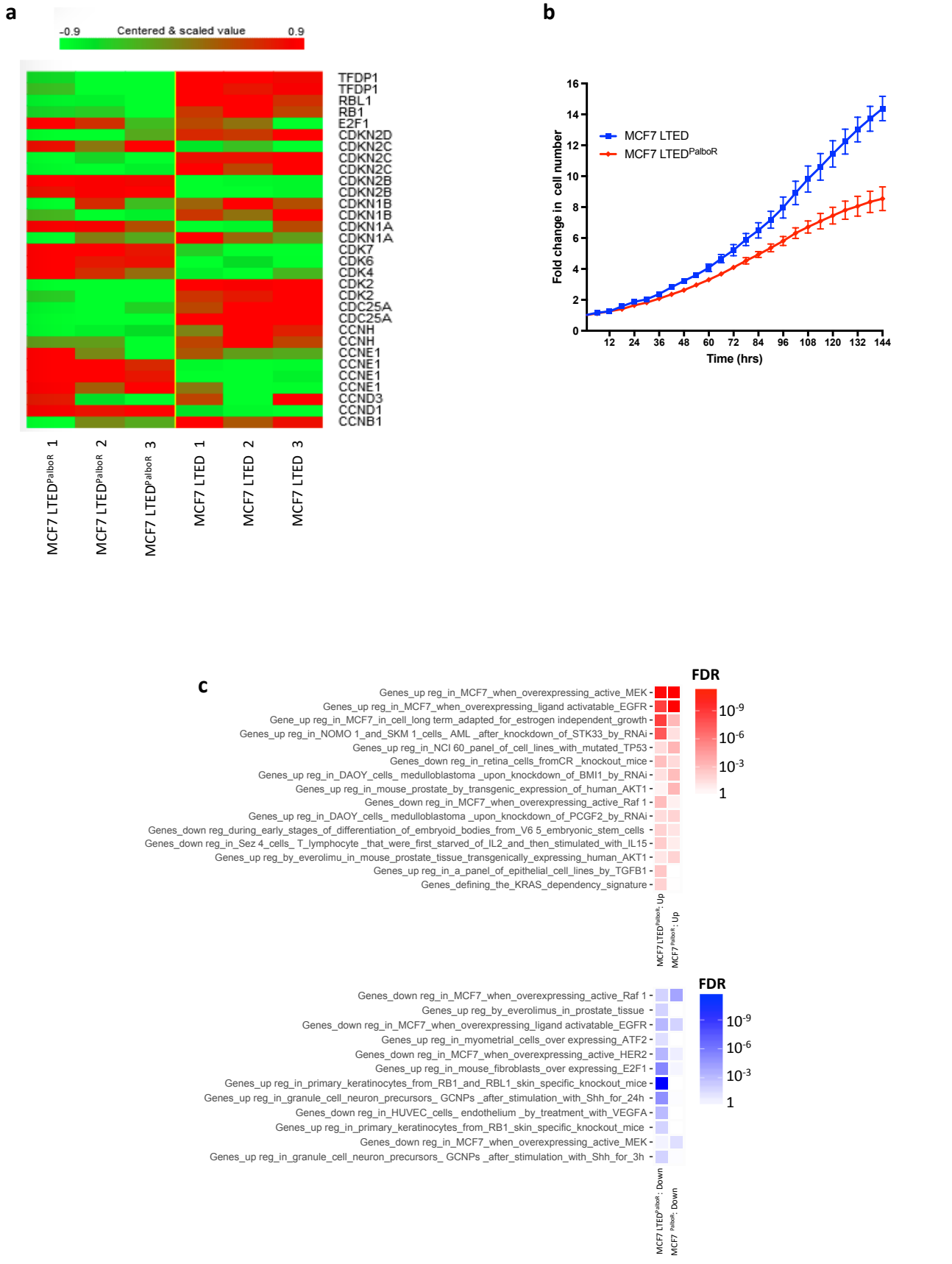

a
MCF7 LTED
MCF7 LTED + Palbo
MCF7 LTED^PalboR + Palbo
CDK1
Cyclin B1
Cyclin A
Tubulin
Cyclin B/CDK1
Cyclin D/CDK4/6
Cyclin E/CDK2
Cyclin A/CDK1
Cyclin A/CDK2
M
G1
G2
S


b
Wilcoxon matched-pairs signed rank test
Stop
Restart
p = 0.0156
p = 0.0078
p = 0.1484
p = 0.0391
Vehicle
Palbociclib
Median Relative Tumour Volume
Days after start treatment
0
1
2
3
0 6 9 13 16 20 23 27 30 34 37 42 48 62 69 76 90 97 106 114 120 127 145 155 162 167 183 188 190 195

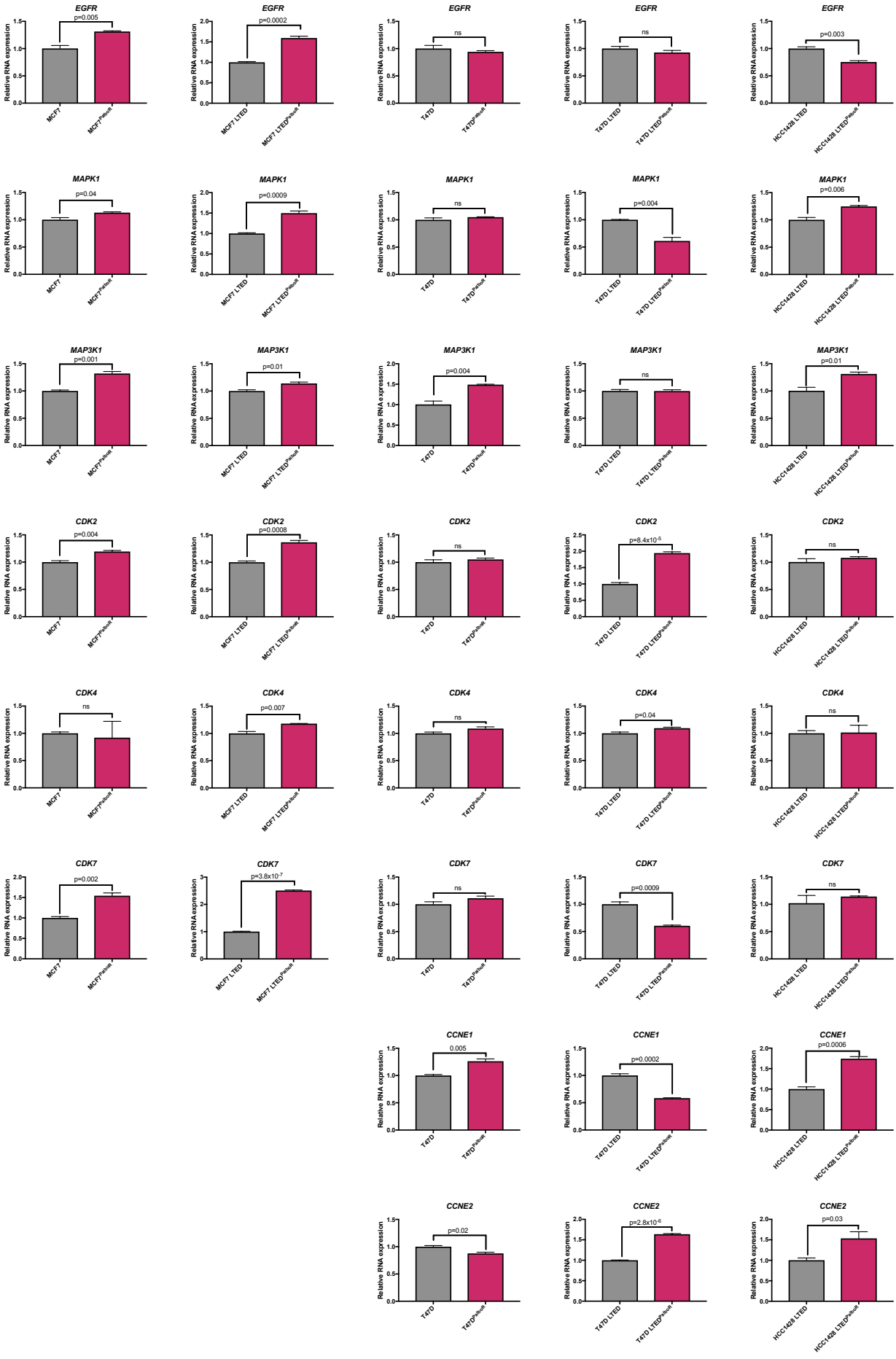

c
RB1
Relative RNA expression
p=0.04
p=0.02
p=6.7x10-6
p=5.8x10-6
p=1.48x10-5
MCF7
MCF7PalboR
MCF7 LTED
MCF7 LTEDPalboR
T47D
T47DPalboR
T47D LTED
T47D LTEDPalboR
HCC1428 LTED
HCC1428 LTEDPalboR


d
MCF7
MCF7PalboR
MCF7PalboR washout
MCF7 LTED
MCF7 LTEDPalboR
MCF7 LTEDPalboR washout
T47D
T47DPalboR
T47DPalboR washout
T47D LTED
T47D LTEDPalboR
T47D LTEDPalboR washout
HCC1428 LTED
HCC1428 LTEDPalboR
HCC1428 LTEDPalboR washout
RB
tubulin

Supp Fig S2

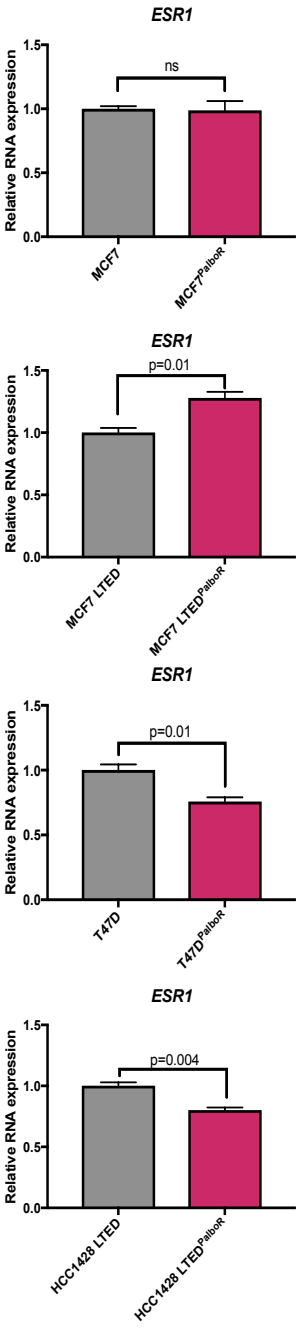

a
-0.9
Centered & scaled value
0.9
TFDP1
TFDP1
RBL1
RB1
E2F1
CDKN2D
CDKN2C
CDKN2C
CDKN2C
CDKN2B
CDKN2B
CDKN1B
CDKN1B
CDKN1A
CDKN1A
CDK7
CDK6
CDK4
CDK2
CDK2
CDC25A
CDC25A
CCNH
CCNH
CCNE1
CCNE1
CCNE1
CCNE1
CCND3
CCND1
CCNB1
MCF7 LTED PalboR 1
MCF7 LTED PalboR 2
MCF7 LTED PalboR 3
MCF7 LTED 1
MCF7 LTED 2
MCF7 LTED 3
b
Fold change in cell number
MCF7 LTED
MCF7 LTED PalboR
Time (hrs)
c
FDR
Genes_up reg_in_MCF7_when_overexpressing_active_MEK
Genes_up reg_in_MCF7_when_overexpressing_ligand activatable_EGFR
Gene_up reg_in_MCF7_in_cell_long term_adapted_for_estrogen independent_growth
Genes_up reg_in_NOMO 1_and_SKM 1_cells_ AML _after_knockdown_of_STK33_by_RNAi
Genes_up reg_in_NCI 60_panel_of_cell_lines_with_mutated_TP53
Genes_down reg_in_retina_cells_fromCR _knockout_mice
Genes_up reg_in_DAOY_cells_ medulloblastoma _upon_knockdown_of_BMI1_by_RNAi
Genes_up reg_in_mouse_prostate_by_transgenic_expression_of_human_AKT1
Genes_down reg_in_MCF7_when_overexpressing_active_Raf 1
Genes_up reg_in_DAOY_cells_ medulloblastoma _upon_knockdown_of_PCGF2_by_RNAi
Genes_down reg_during_early_stages_of_differentiation_of_embryoid_bodies_from_V6 5_embryonic_stem_cells
Genes_down reg_in_Sez 4_cells_ T_lymphocyte _that_were_first_starved_of_IL2_and_then_stimulated_with_IL15
Genes_up reg_by_everolimu_in_mouse_prostate_tissue_transgenically_expressing_human_AKT1
Genes_up reg_in_a_panel_of_epithelial_cell_lines_by_TGFB1
Genes_defining_the_KRAS_dependency_signature
MCF7 LTED PalboR: Up
MCF7 PalboR: Up
FDR
Genes_down reg_in_MCF7_when_overexpressing_active_Raf 1
Genes_up reg_by_everolimus_in_prostate_tissue
Genes_down reg_in_MCF7_when_overexpressing_ligand activatable_EGFR
Genes_up reg_in_myometrial_cells_over expressing_ATF2
Genes_down reg_in_MCF7_when_overexpressing_active_HER2
Genes_up reg_in_mouse_fibroblasts_over expressing_E2F1
Genes_up reg_in_primary_keratinocytes_from_RB1_and_RBL1_skin_specific_knockout_mice
Genes_up reg_in_granule_cell_neuron_precursors_ GCNPs _after_stimulation_with_Shh_for_24h
Genes_down reg_in_HUVEC_cells_ endothelium _by_treatment_with_VEGFA
Genes_up reg_in_primary_keratinocytes_from_RB1_skin_specific_knockout_mice
Genes_down reg_in_MCF7_when_overexpressing_active_MEK
Genes_up reg_in_granule_cell_neuron_precursors_ GCNPs _after_stimulation_with_Shh_for_3h
MCF7 LTED PalboR: Down
MCF7 PalboR: Down

Supp Fig S3


EGFR
p=0.005
MCF7
MCF7^Palbo/R
EGFR
p=0.0002
MCF7 LTED
MCF7 LTED^Palbo/R
EGFR
ns
T47D
T47D^Palbo/R
EGFR
ns
T47D LTED
T47D LTED^Palbo/R
EGFR
p=0.003
HCC1428 LTED
HCC1428 LTED^Palbo/R
MAPK1
p=0.04
MCF7
MCF7^Palbo/R
MAPK1
p=0.0009
MCF7 LTED
MCF7 LTED^Palbo/R
MAPK1
ns
T47D
T47D^Palbo/R
MAPK1
p=0.004
T47D LTED
T47D LTED^Palbo/R
MAPK1
p=0.006
HCC1428 LTED
HCC1428 LTED^Palbo/R
MAP3K1
p=0.001
MCF7
MCF7^Palbo/R
MAP3K1
p=0.01
MCF7 LTED
MCF7 LTED^Palbo/R
MAP3K1
p=0.004
T47D
T47D^Palbo/R
MAP3K1
ns
T47D LTED
T47D LTED^Palbo/R
MAP3K1
p=0.01
HCC1428 LTED
HCC1428 LTED^Palbo/R
CDK2
p=0.004
MCF7
MCF7^Palbo/R
CDK2
p=0.0008
MCF7 LTED
MCF7 LTED^Palbo/R
CDK2
ns
T47D
T47D^Palbo/R
CDK2
p=8.4x10-5
T47D LTED
T47D LTED^Palbo/R
CDK2
ns
HCC1428 LTED
HCC1428 LTED^Palbo/R
CDK4
ns
MCF7
MCF7^Palbo/R
CDK4
p=0.007
MCF7 LTED
MCF7 LTED^Palbo/R
CDK4
ns
T47D
T47D^Palbo/R
CDK4
p=0.04
T47D LTED
T47D LTED^Palbo/R
CDK4
ns
HCC1428 LTED
HCC1428 LTED^Palbo/R
CDK7
p=0.002
MCF7
MCF7^Palbo/R
CDK7
p=3.8x10-7
MCF7 LTED
MCF7 LTED^Palbo/R
CDK7
ns
T47D
T47D^Palbo/R
CDK7
p=0.0009
T47D LTED
T47D LTED^Palbo/R
CDK7
ns
HCC1428 LTED
HCC1428 LTED^Palbo/R
CCNE1
0.005
T47D
T47D^Palbo/R
CCNE1
p=0.0002
T47D LTED
T47D LTED^Palbo/R
CCNE1
p=0.0006
HCC1428 LTED
HCC1428 LTED^Palbo/R
CCNE2
p=0.02
T47D
T47D^Palbo/R
CCNE2
p=2.8x10-6
T47D LTED
T47D LTED^Palbo/R
CCNE2
p=0.03
HCC1428 LTED
HCC1428 LTED^Palbo/R
Relative RNA expression

Supp Fig S4

a



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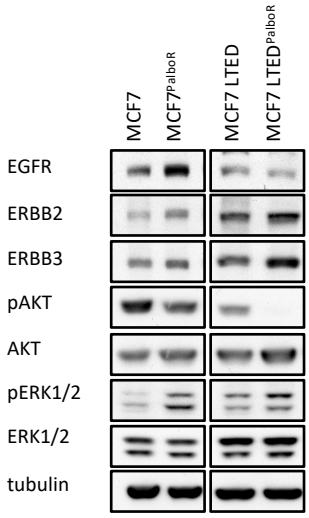
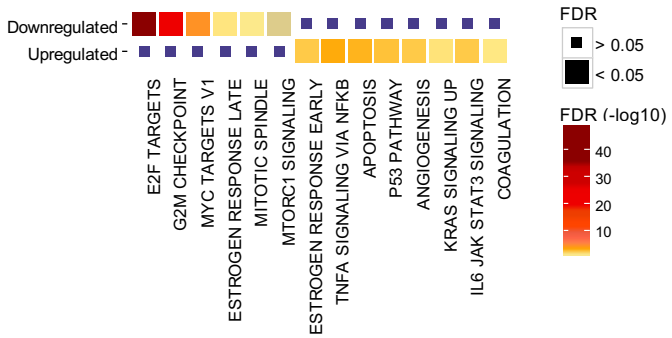


Supp Fig S5

a



b

source	term name Gene Ontology (Biological process)	term ID	n. of term genes	n. of query genes	n. of common genes	corrected p-value
BP	cellular response to stimulus	GO:0051716	7303	57	38	2.01e-02
BP	body fluid secretion	GO:0007589	91	57	5	1.61e-02
BP	system development	GO:0048731	4669	57	30	7.29e-03
BP	animal organ development	GO:0048513	3415	57	25	8.61e-03
BP	gland development	GO:0048732	437	57	9	1.10e-02
BP	epithelium development	GO:0060429	1262	57	15	5.62e-03
BP	cell cycle	GO:0007049	1829	57	17	2.85e-02
BP	mitotic cell cycle	GO:0000278	985	57	16	3.30e-05
BP	mitotic cell cycle process	GO:1903047	821	57	12	8.67e-03
BP	positive regulation of developmental process	GO:0051094	1274	57	14	3.22e-02
BP	growth	GO:0040007	968	57	12	4.58e-02
source	term name Protein databases (CORUM protein complexes)	term ID	n. of term genes	n. of query genes	n. of common genes	corrected p-value
cor	PDZK1-NHERF1-EZR complex	CORUM:6793	3	13	2	1.50e-02
source	term name Biological pathways (Reactome)	term ID	n. of term genes	n. of query genes	n. of common genes	corrected p-value
rea	Signaling by Nuclear Receptors	R-HSA-9006931	198	41	7	3.24e-03
rea	ESR-mediated signaling	R-HSA-8939211	155	41	6	8.99e-03
rea	Estrogen-dependent gene expression	R-HSA-9018519	149	41	6	7.19e-03

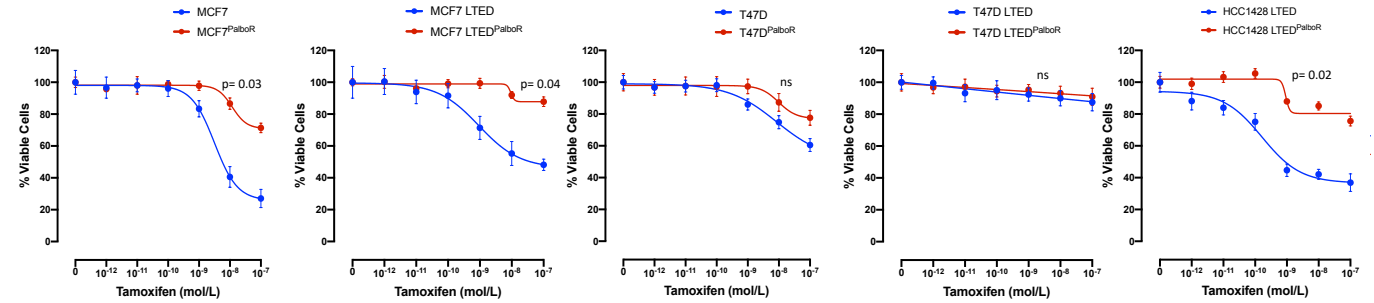
c

source	term name Gene Ontology (Biological process)	term ID	n. of term genes	n. of query genes	n. of common genes	corrected p-value
BP	response to water	GO:0009415	16	71	4	9.76e-04
BP	response to hydrostatic pressure	GO:0051599	7	71	3	5.46e-03
BP	biological adhesion	GO:0022610	1330	71	19	6.55e-04
BP	cell adhesion	GO:0007155	1323	71	18	3.03e-03
BP	cell-cell adhesion	GO:0098609	763	71	13	1.18e-02
BP	regulation of cell adhesion	GO:0030155	628	71	14	1.81e-04
BP	regulation of cell-cell adhesion	GO:0022407	372	71	9	2.83e-02
BP	negative regulation of cell adhesion	GO:0007162	242	71	8	9.59e-03
BP	regulation of cell death	GO:0010941	1645	71	19	1.62e-02
BP	regulation of biological quality	GO:0065008	3633	71	29	4.42e-02
BP	response to organic cyclic compound	GO:0014070	941	71	14	2.26e-02
BP	response to endogenous stimulus	GO:0009719	1570	71	19	8.13e-03
BP	multicellular organismal process	GO:0032501	7343	71	47	4.26e-03
BP	developmental process	GO:0032502	6118	71	43	1.54e-03
BP	anatomical structure development	GO:0048856	5699	71	40	6.82e-03
BP	multicellular organism development	GO:0007275	5232	71	38	6.78e-03
BP	system development	GO:0048731	4669	71	36	3.73e-03
BP	animal organ development	GO:0048513	3415	71	31	1.02e-03
BP	gland development	GO:0048732	437	71	10	1.40e-02
BP	cellular developmental process	GO:0048869	4229	71	32	3.65e-02
BP	cell differentiation	GO:0030154	4057	71	31	4.55e-02
BP	myeloid leukocyte differentiation	GO:0002573	193	71	7	2.28e-02
BP	positive regulation of metabolic process	GO:0009893	3254	71	28	1.58e-02
BP	positive regulation of macromolecule metabolic process	GO:0010604	3017	71	26	4.06e-02
BP	positive regulation of nitrogen compound metabolic process	GO:0051173	2889	71	27	5.18e-03
BP	positive regulation of cellular metabolic process	GO:0031325	3001	71	28	3.07e-03
source	term name Protein databases (CORUM protein complexes)	term ID	n. of term genes	n. of query genes	n. of common genes	corrected p-value
cor	TFAP2C-Myc-KDM5B complex	CORUM:6203	3	19	2	4.95e-02
source	term name Biological pathways (Reactome)	term ID	n. of term genes	n. of query genes	n. of common genes	corrected p-value
rea	Signaling by NOTCH	R-HSA-157118	126	54	7	1.06e-03
source	term name Regulatory motifs in DNA (TRANSFAC TFBS)	term ID	n. of term genes	n. of query genes	n. of common genes	corrected p-value
tf	Factor: SP1; motif: GGGGYGGGGNS	TF:M01303	7863	71	46	3.75e-02
tf	Factor: SP1; motif: GGGGYGGGGNS; match class: 0	TF:M01303_0	7863	71	46	3.75e-02

[?] Gene Ontology — Biological process, Cellular component, Molecular function
Inferred from experiment [IDA, IPI, IMP, IGI, IEP]
Direct assay [IDA] / Mutant phenotype [IMP]
Genetic interaction [IGI] / Physical interaction [IPI]
Traceable author [TAS] / Non-traceable author [NAS] / Inferred by curator [IC]
Expression pattern [IEP] / Sequence or structural similarity [ISS] / Genomic context [IGC]
Biological aspect of ancestor [IBA] / Rapid divergence [IRD]
Reviewed computational analysis [RCA] / Electronic annotation [IEA]
No biological data [ND] / Not annotated or not in background [NA]
Biological pathways — KEGG, Reactome
[?] Regulatory motifs in DNA — TRANSFAC TFBS
[?] Protein databases — Human Protein Atlas, CORUM protein complexes
[?] Human Phenotype Ontology (sequence homologs in other species)

Supp Fig S6

a



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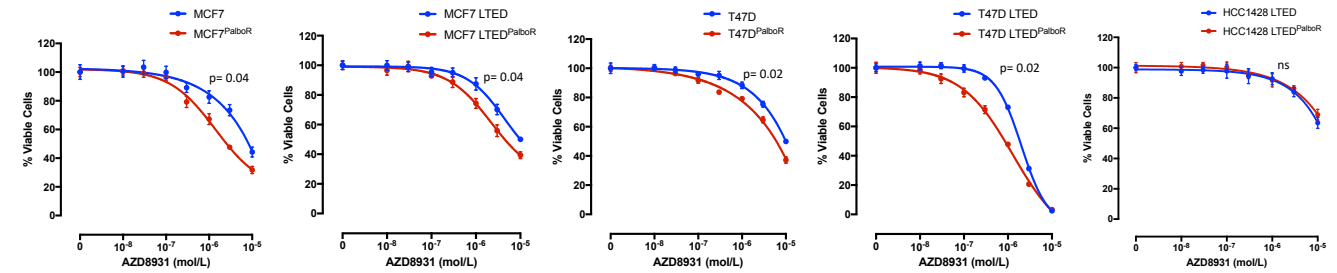

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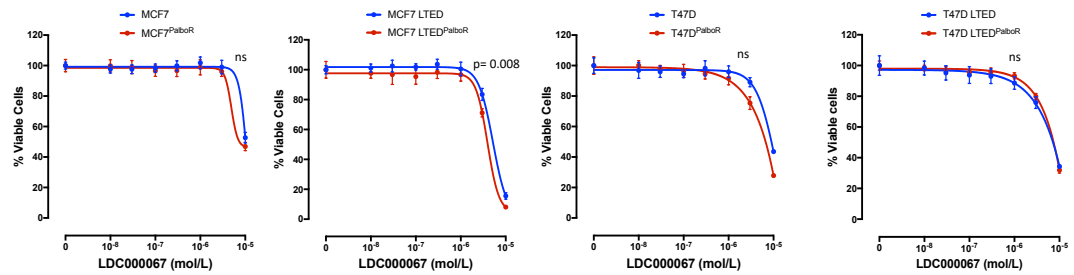

Supp Fig S7