Supplemental Figures

Figure S1

Patient-derived organoids responses to oxaliplatin.

(A) Representative images from CRC240, CRC159, and CRC344 organoids treated with DMSO or oxaliplatin (20 μM) for 6 days. Scale bar = 400 μm.

Figure S2

Transcriptomic and chromatin accessibility signatures of oxaliplatin treatment cells and parental cells.

(A) Left: boxplots showing the global distribution of normalized read counts in triplicates of three CRC orgnoids with oxaliplatin or DMSO treatments. Right: principal component analysis (PCA) of all samples profiled in RNA-Seq. Samples from different patients are presented in different shapes, and treatments are color-coded (red: samples treated with oxaliplatin, green: samples treated with DMSO).

(B) Volcano plot showing differential expressions of genes in organoids with oxaliplatin treatment compared to control (DMSO) organoids in CRC240, CRC159, and CRC344 respectively. Red and blue points represent the genes with significantly increased (FDR<0.05, log2FC>1) and decreased expression, (FDR<0.05, log2FC<-1) respectively, post-oxaliplatin treatment

(C) Heatmaps of ATAC-Seq signals covers genomic regions ± 1kb across the TSS of genes showing open chromatin accessibility in genome-wide scale. Color map shows the intensity of ATAC-Seq signals.

(D) MA plot of log2 fold change versus mean peaks signal showing ATAC-seq differential peaks in organoids with oxaliplatin treatment compared to control (DMSO) organoids in CRC240, CRC159, and CRC344, respectively. ATAC-seq peaks that display significant increases post-treatment (p.val < 0.05, log2FC>1) are shown in red color, while significantly decreased peaks (p.val < 0.05, log2FC<-1) are shown in blue.

Figure S3

FGFR1 and OXTR are upregulated in CRC oxaliplatin resistant organoids.

(A) Left: RT-qPCR showed mRNA expression of FGFR1 in three cancer organoids with control (DMSO) and oxaliplatin treatment. Right: mRNA expression of OXTR in FGFR1 in three cancer organoids with control (DMSO) and oxaliplatin treatment. Organoids were exposed to the IC50 concentration of oxaliplatin. Expression levels are given relative to the housekeeping gene GAPDH. Data were mean ± SEM (n=3) and the statistical significance was assessed by unpaired two-tailed student's *t*-test. *p<0.05; ***p<0.001; n.s., not significant. (B) ATAC-Seq peaks associated with FGFR1 and OXTR in CRC240, CRC159, and CRC344 organoids. The peaks were visualized using UCSC genome browser, and gray dash lines indicating the regions of differential peaks identified in CRC240 organoids. Only CRC240 shows significantly increase of ATAC-Seq signal in the peak regions after oxaliplatin treatment (p.val < 0.05). (C) Normalized read counts of FGFR1 and OXTR from RNASeq. Only CRC240 shows significantly upregulated expressions of FGFR1 and OXTR (p.val < 0.05, log2FC > 1) (D) Bright-field image of CRC119 organoid. Scale bar = 400 μm. (E) Dose-response curve of oxaliplatin treatment in CRC119 organoids. Organoids were exposed to oxaliplatin for 6 days, and cell viability was determined by CellTiter-Glo 3D cell

viability assay. The IC50 values were calculated by a nonlinear regression model in GraphPad Prism. Error bars represents the standard error of the mean.

(F) Protein expression was assessed by western blot using antibodies of FGFR1, phospho-FGFR1, FGFR2, FGFR3, FGFR4, OXTR, and beta-tubulin in CRC119 with DMSO or oxaliplatin treatment .

Figure S4

Inhibition of FGFR1/OXTR is active against CRC240 organoids.

(A) Dose-response curve of CRC240 treated with PD166866 or L368,899. Cell viability was measured on day 7 using CellTiter Glo 3D cell viability assay. The IC50 values were calculated by a nonlinear regression model in GraphPad Prism.

(B) CRC159, CRC344, and CRC119 organoids were treated with IC50 values of oxaliplatin, PD166866, L368,899 or a combination of two agents. Cell viability assay was performed on day 7 and viability values are shown in relation to control (DMSO).

(C) Left: Combination index (CI) values for CRC240 organoids treated with PD and OXA in combination at doses of 8.5, 17, 34, 68, and 136 μM (PD), and 32, 64, 128, 255, and 510 μM (OXA). Right: Combination Index (CI) values for CRC240 organoids treated with L368 and OXA in combination at doses of 8, 16, 32, 64, and 128 μM (L368) and 32, 64, 128, 255, 510 μM (OXA). CI values ≤ 0.9 indicate synergism, a CI value >0.9 and <1.1 indicates an additive effect, and CI values ≥ 1.1 indicate antagonism. Combination index (CI) values calculated from data of viability assay using CompuSyn software.

Figure S5

Predicted transcriptional factors binding sites within FGFR1 and OXTR peaks.

Left: Venn diagram showing 8 TFs shared by peaks in both genes, 4 TFs unique within FGFR1 peaks and 8 TFs unique within OXTR peaks. Right: list of shared and unique TFs within FGFR1 and OXTR peaks.

Figure S6

Binding motif analysis of predicted binding transcriptional factors.

Binding motifs of TFs predicted in Figure S5. Only the TFs with available binding motifs in MotifMaps are shown.

Figure S1

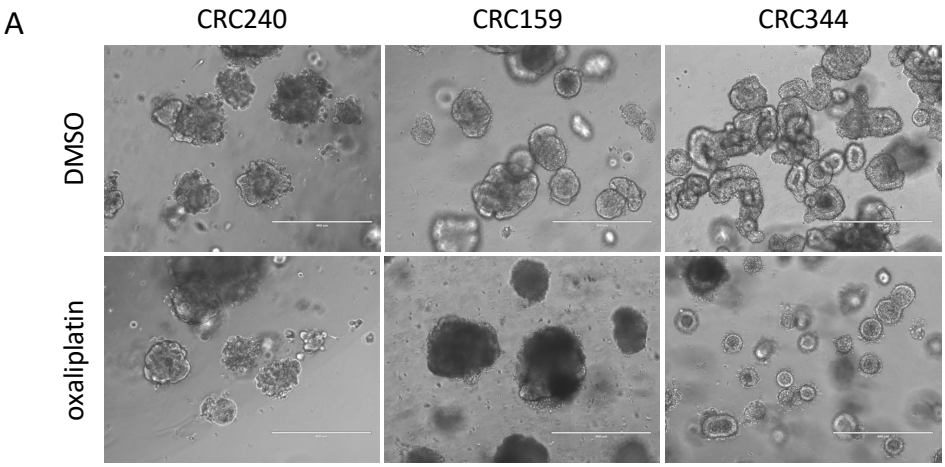
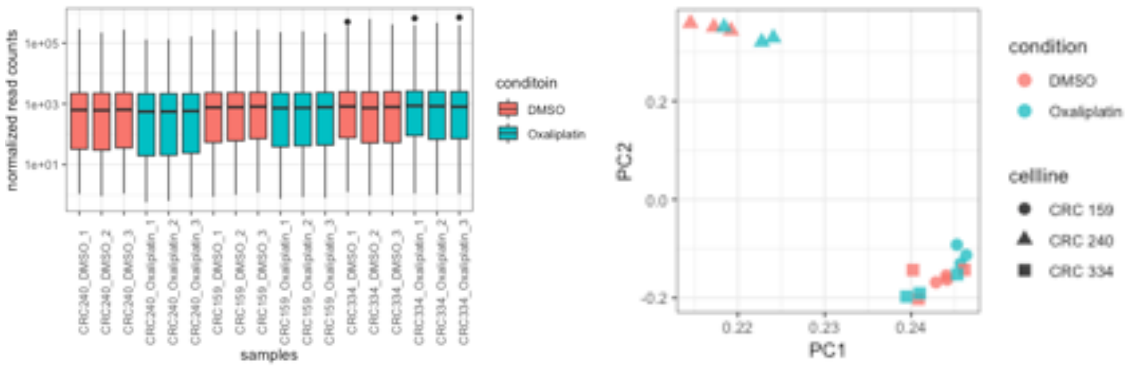


Figure S2

A



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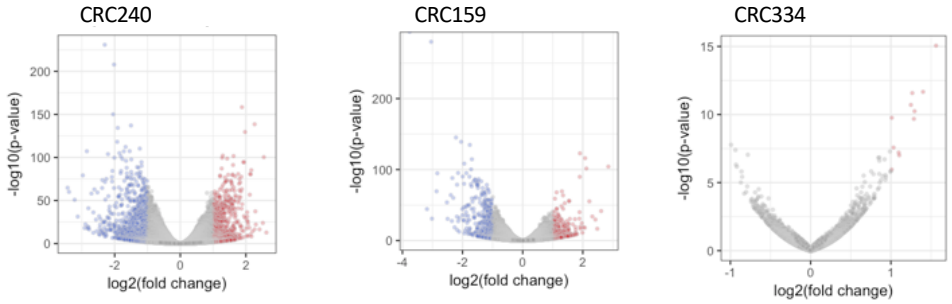

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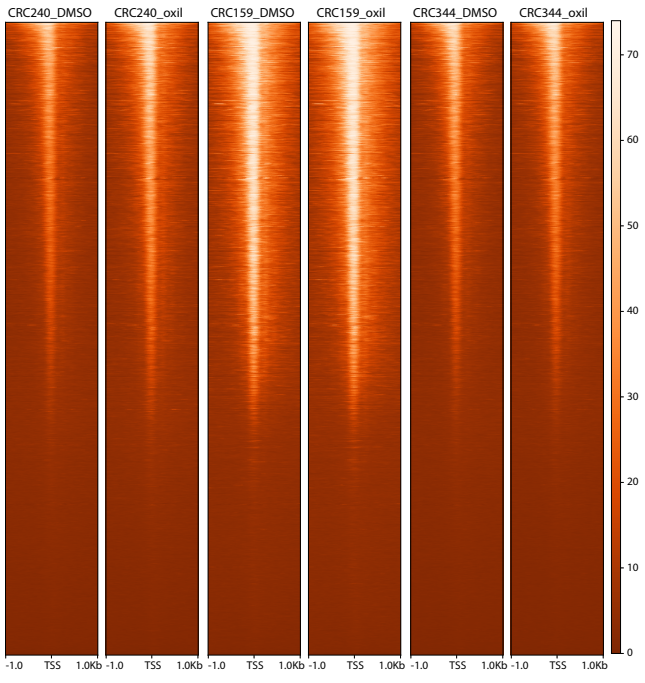

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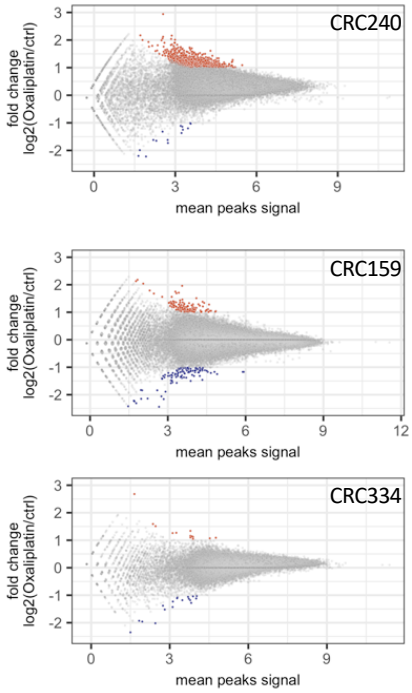


Figure S3

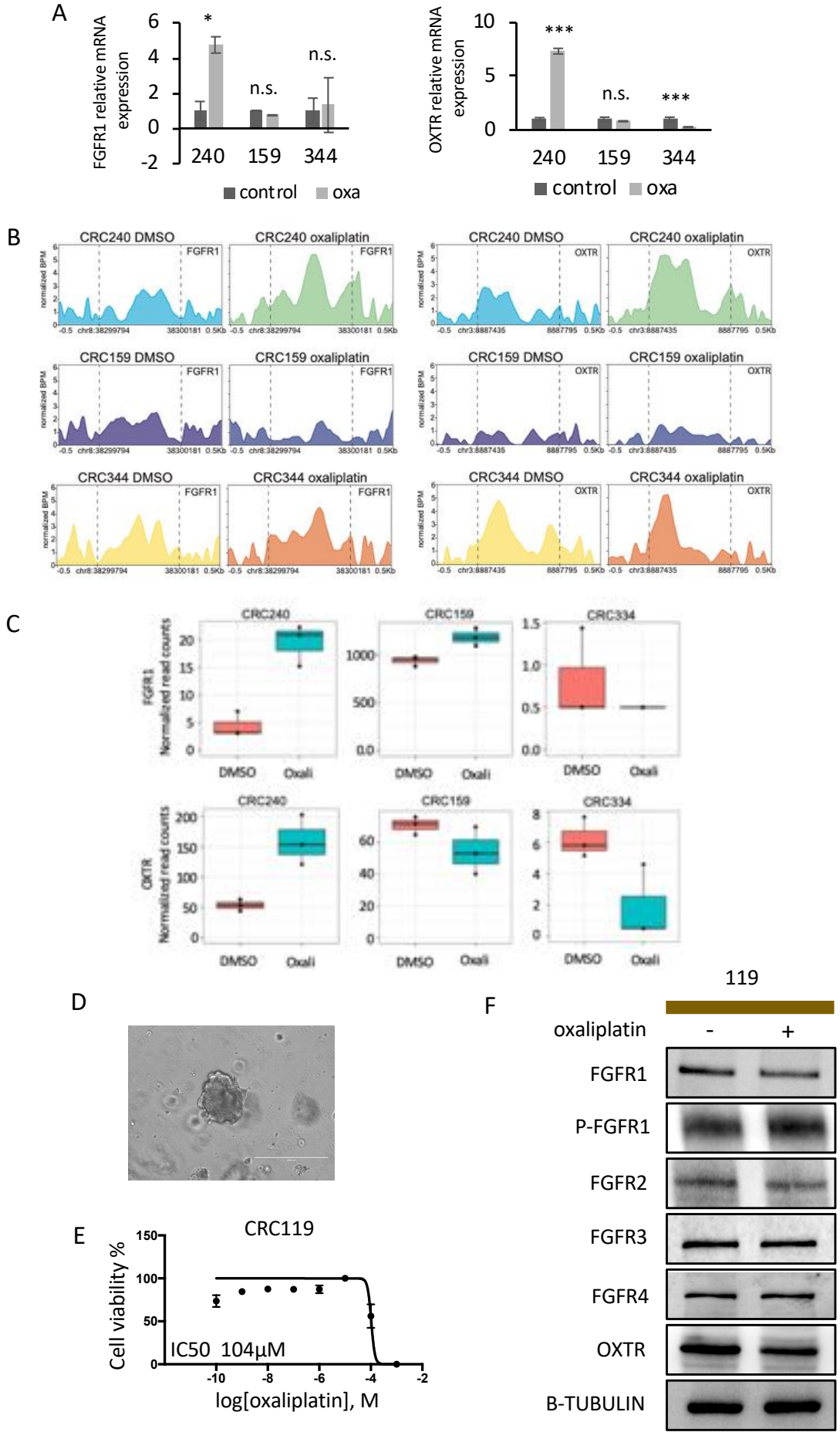
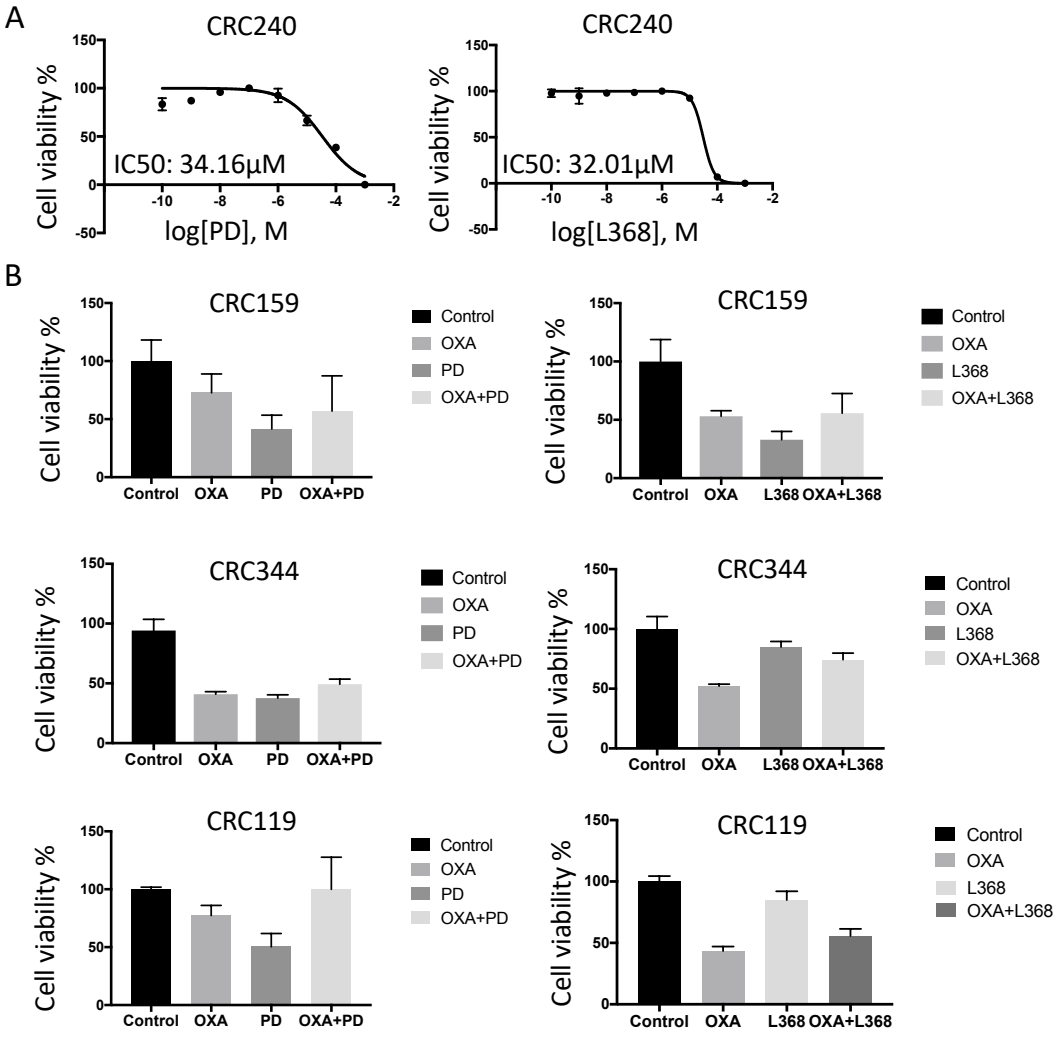

A
FGFR1 relative mRNA expression
6
4
2
0
-2
*
n.s.
n.s.
240
159
344
control
oxa
OXTR relative mRNA expression
10
5
0
***
n.s.
***
240
159
344
control
oxa
B
CRC240 DMSO
CRC240 oxaliplatin
CRC159 DMSO
CRC159 oxaliplatin
CRC344 DMSO
CRC344 oxaliplatin
FGFR1
OXTR
normalized BPM
C
CRC240
CRC159
CRC334
FGFR1 Normalized read counts
OXTR Normalized read counts
DMSO
Oxali
D
E
CRC119
Cell viability %
IC50 104μM
log[oxaliplatin], M
F
119
oxaliplatin
-
+
FGFR1
P-FGFR1
FGFR2
FGFR3
FGFR4
OXTR
B-TUBULIN

Figure S4



C

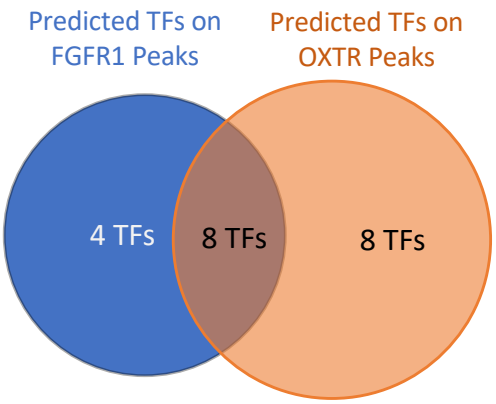
OXA (μM)

PD (μM)	32	64	128	255	510
8.5	0.56	0.8	1.06	1.49	1.83
17	0.66	0.84	1	1.13	1.6
34	0.5	0.58	0.63	0.78	1.12
68	0.38	0.62	0.39	0.36	0.64
136	0.49	0.49	0.54	0.42	0.41

OXA (μM)

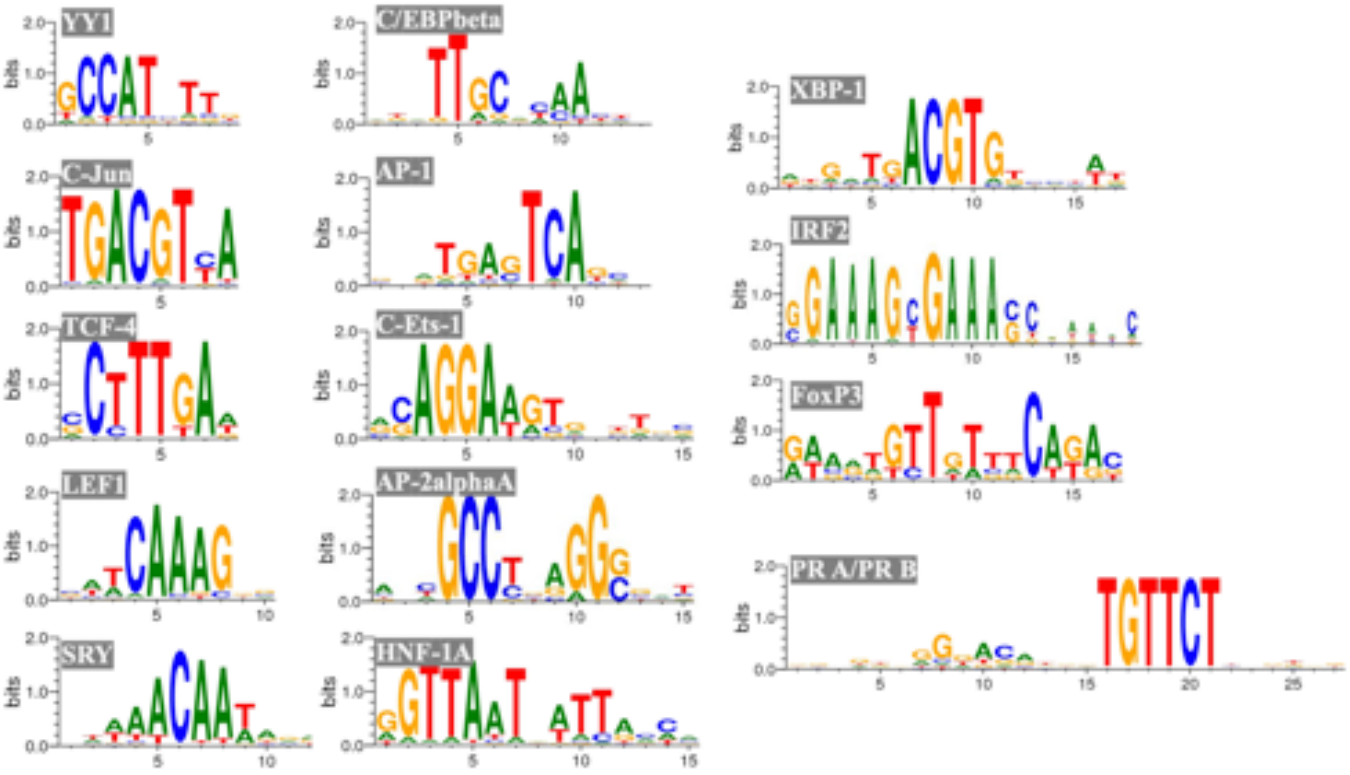
L368 (μM)	32	64	128	255	510
8	0.73	1.1	1.37	0.98	1.02
16	0.62	0.58	0.74	0.86	1.1
32	0.75	0.71	0.58	0.9	1.15
64	0.23	0.23	0.23	0.23	0.41
128	0.6	0.46	0.46	0.15	0.46

Figure S5



TFs on FGFR1 Peaks	Common TFs	TFs on OXTR Peaks
TCF-4E	C/EBPbeta	AP-1
AP-2alpha	YY1	c-Jun
HNF-1A	c-Ets-1	LEF-1
XBP-1	GR-beta	IRF-2
	GR-alpha	TFIID
	ER-alpha	SRY
	TFII-I	PR B
	FOXP3	PR A

Figure S6


YY1
C/EBPbeta
XBP-1
C-Jun
AP-1
IRF2
TCF-4
C-Ets-1
FoxP3
LEF1
AP-2alphaA
PR A/PR B
SRY
HNF-1A
bits