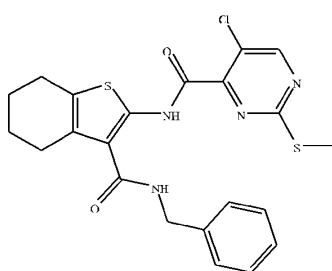


ID	Structure	MW (g/mol)	-logP ²⁵ /logD ²⁵ (pH=7.4)	TPSA ⁴⁰	LogS ⁴¹ /Solubility μM (pH=7.4) T= 298K UV-Vis	glide XP score	ΔG _{res} (kcal/mol) (pH=7.4) T=300K M±SE	ΔG _{apo} (kcal/mol) (pH=7.4) T= 300K M±SD	TR-FRET iC ₅₀ (nM) (pH=7.4) T= 293K M±SD	LipE _{apo} /LipE _{apo}
1		477.59	4.01/4.65	80.89	-6.12/12.86	-7.71	-12.15±1.57	-12.49±0.29	1.63±0.01	5.09/4.45
2		473.01	3.79/5.45	137.52	-6.06/≤1	-11.53	-11.31±0.58	-11.63±1.15	0.40±0.00	4.68/3.02
3		515.07	3.13/3.28	180.04	-5.30/40.24	-8.05	-10.94±1.44	-9.75±0.43	4.45±0.20	3.97/3.82
4		422.54	3.34/4.72	104.26	-5.78/≤1	-11.1	N/A	-11.38±0.66	1.47±0.14	4.95/3.57
5		457.60	4.09/5.06	80.89	-6.03/10.55	-7.57	-12.52±1.20	-10.72±0.34	3.80±0.24	3.72/2.75
6		415.52	3.63/3.59	80.89	-5.11/27.70	-9.52	-12.08±1.36	-10.20±0.91	2.46±0.11	3.80/3.84
7		382.40	2.62/4.43	86.44	-5.07/28.80	-9.45	N/A	-10.19±1.03	2.07±0.02	4.80/2.99
8		452.59	3.61/4.92	137.52	-5.56/3.23	-8.79	-9.8±0.49	-10.21±0.99	0.69±0.04	3.83/2.52
9		411.56	3.08/4.33	89.68	-5.03/19.71	-10.92	-9.46±0.58	-10.28±0.58	2.15±0.04	4.41/3.16
10		426.57	3.39/3.06	92.92	-4.46/99.32	-11.37	-13.66±1.58	-12.51±1.00	1.17±0.00	5.72/6.05
11		425.59	3.26/4.57	89.68	-5.38/12.43	-11.1	-11.81±1.58	-10.19±0.02	4.50±0.15	4.16/2.85
ref	gsk2981278*	461.61	4.28/4.11	84.45	N/A	N/A	N/A	-11.22±0.90	1.71±0.16	3.89/4.06

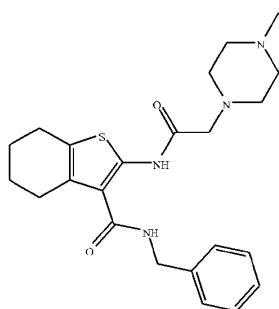
Fig. 1A

ID ^a	Structure	MW (g/mol)	$\log P^{b1}$ $\log D$ (pH=7.4)	TPSA ^{b1}	$\log S^{c1}$ /Solubility μM (pH=7.4) T= 298K UV	glide XP score	ΔG_{ref} (kcal/mol) (pH=7.4) T=300K M±SE	ΔG_{exp} (kcal/mol) (pH=7.4) T= 300K M±SD	TN-FRET IC ₅₀ (nM) (pH=7.4) T= 293K M±SD	LipE _{exp} /LipE _{agp}
12		369.48	2.93/3.68	90.54	-4.55/31.28	-10.01	N/A	-7.57±0.75	3.51±0.08	2.58/1.83
13		397.53	3.30/4.45	90.54	-5.20/26.97	-9.49	-10.09±0.93	-12.69±0.80	0.23±0.00	5.94/4.79
14		399.51	2.45/3.08	119.56	-4.36/29.42	-8.56	-10.54±1.61	-12.73±0.29	1.76±0.11	6.82/6.19
15		383.51	3.00/4.05	90.54	-4.78/32.88	-7.01	-10.09±0.92	-10.39±0.87	5.66±0.27	4.57/3.52
16		440.58	3.45/4.44	129.56	-5.10/8.05	-9.31	-9.94±0.49	-11.53±1.86	8.98±0.76	3.89/2.90
17		385.48	2.69/2.60	110.77	-3.80/79.33	-7.05	-10.04±1.57	-6.16±0.04	45.82±2.31	4.98/5.07
18		400.49	2.42/3.00	112.66	-3.96/34.82	-6.96	-10.47±0.49	-7.78±0.56	20.14±0.96	2.07/1.49
19		396.47	2.41/1.62	130.04	-3.75/93.59	-8.64	-13.32±1.07	-13.35±0.83	3.43±0.23	3.26/4.05
20		354.43	2.38/2.85	123.12	-3.83/90.93	-8.33	-10.31±0.78	-8.85±0.94	13.31±0.30	2.93/2.46
21		398.52	2.56/0.40	111.36	-4.07/84.70	-5.84	-13.75±1.31	-7.29±0.44	57.25±4.80	3.89/6.05
22		363.43	2.41/4.15	100.19	-4.82/18.34	-9.52	-10.06±1.44	-10.07±0.81	19.61±0.54	4.92/3.17
23		455.55	2.82/3.94	142.71	-5.47/51	-10.79	-8.44±0.91	-10.06±0.72	16.59±1.20	6.91/5.79
ref	gsk2981278*	461.61	4.28/4.11	84.45	N/A	N/A	N/A	-11.22±0.90	1.71±0.16	3.89/4.06

Fig. 1B

**Compound 2**

N-(3-(benzylcarbamoyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-chloro-2-(methylthio)pyrimidine-4-carboxamide

Fig. 2**Cpd 10**

N-benzyl-2-(2-(4-methylpiperazin-1-yl)acetamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide

Fig. 3

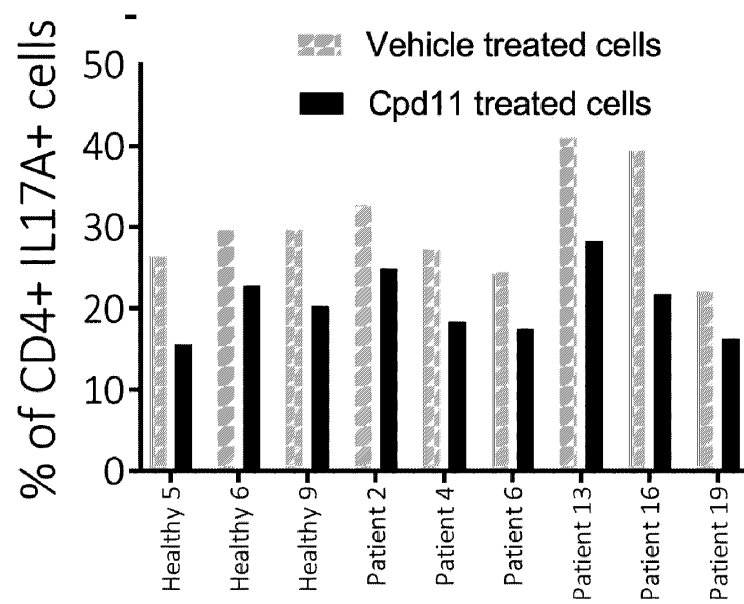


Fig. 4

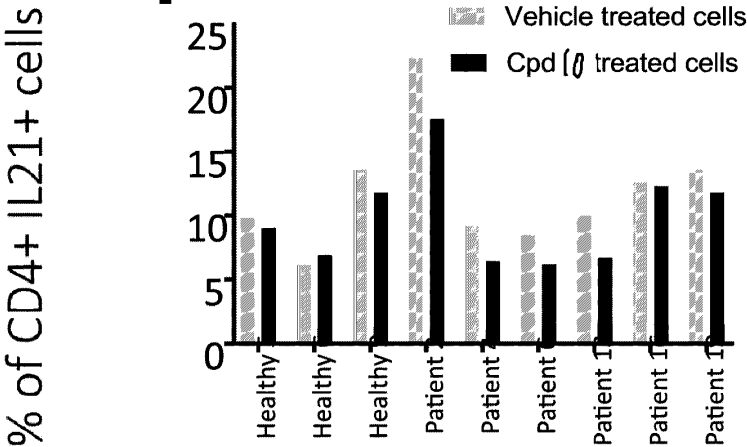


Fig. 5

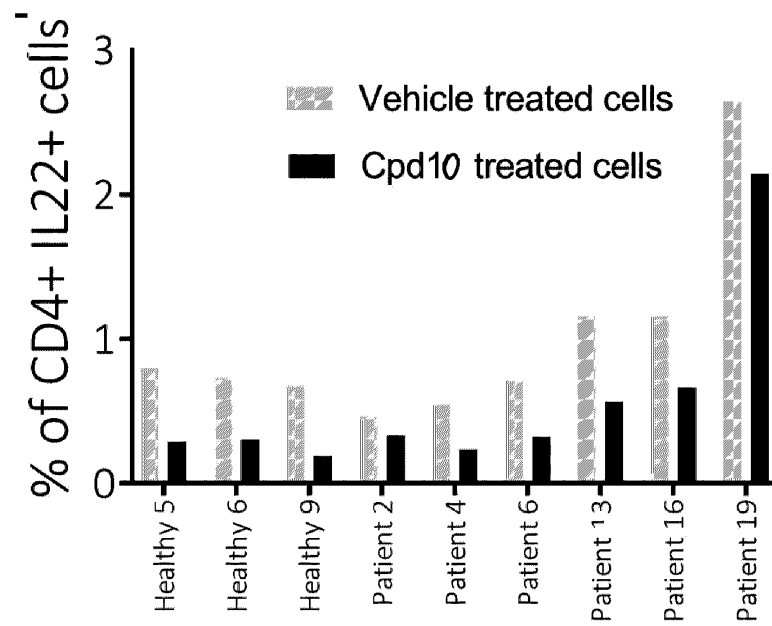


Fig. 6

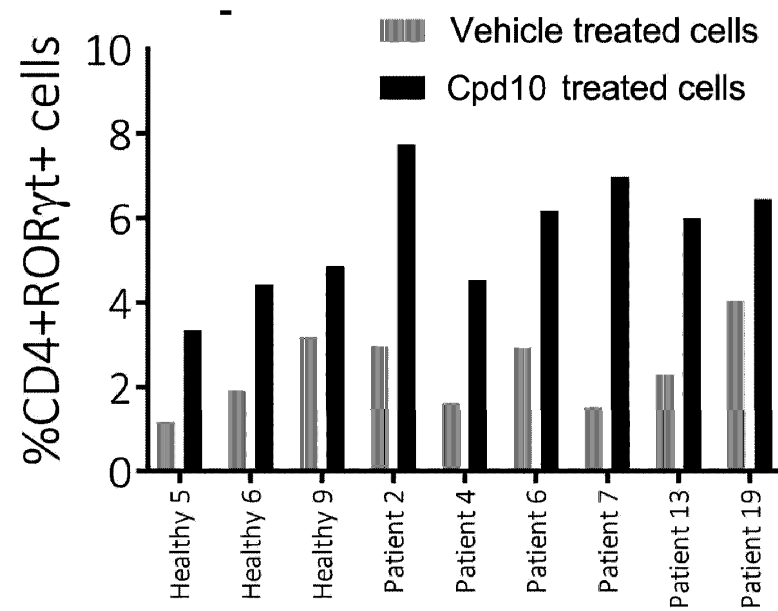


Fig. 7

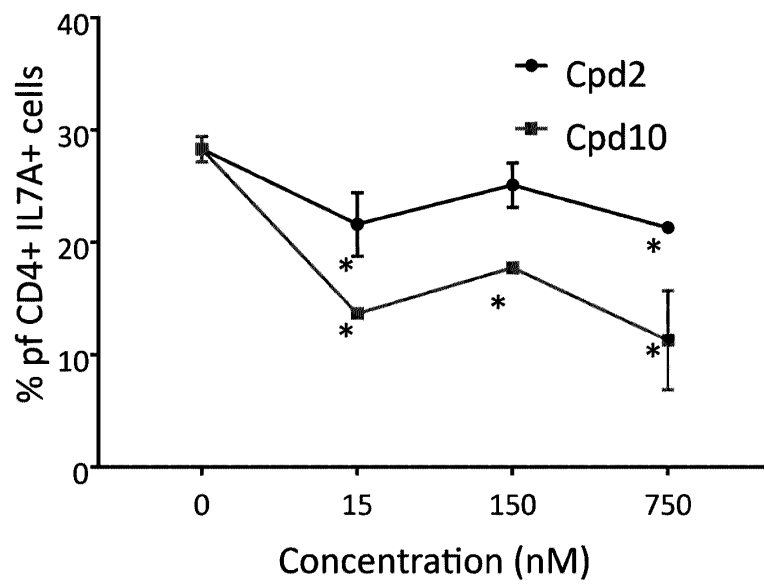


Fig. 8

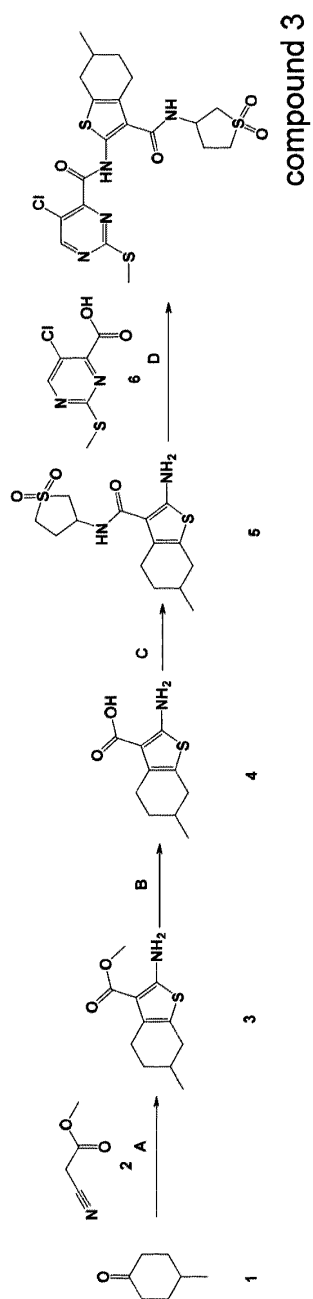


Fig. 9

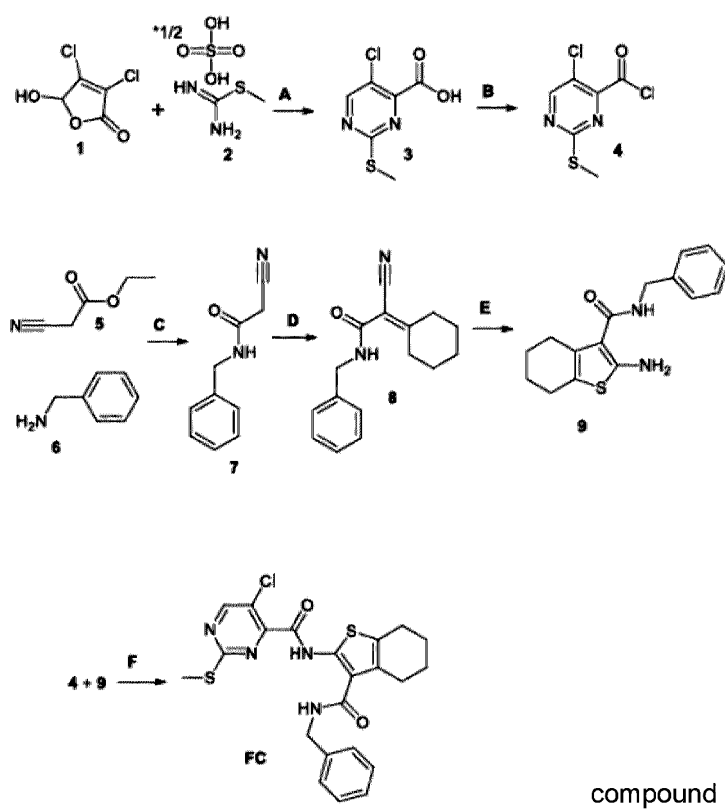


Fig. 10

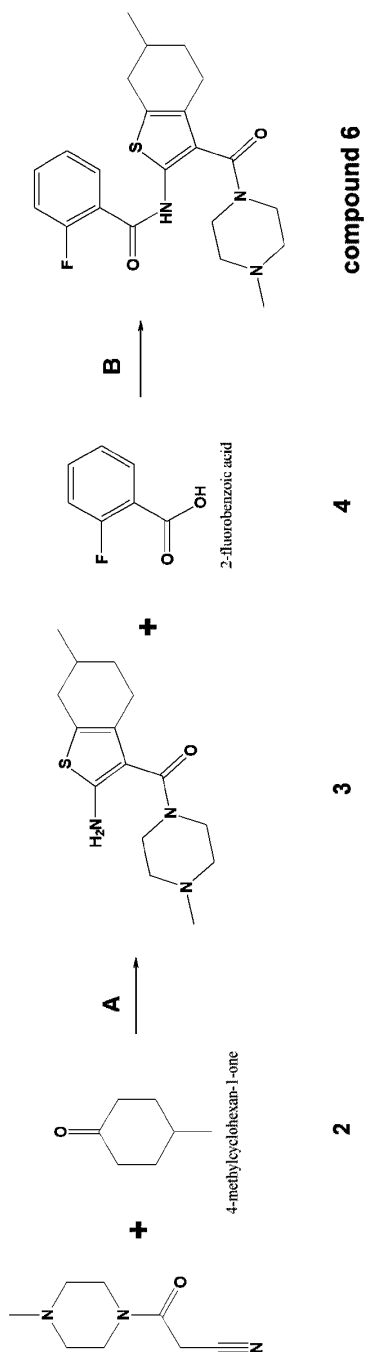


Fig. 11

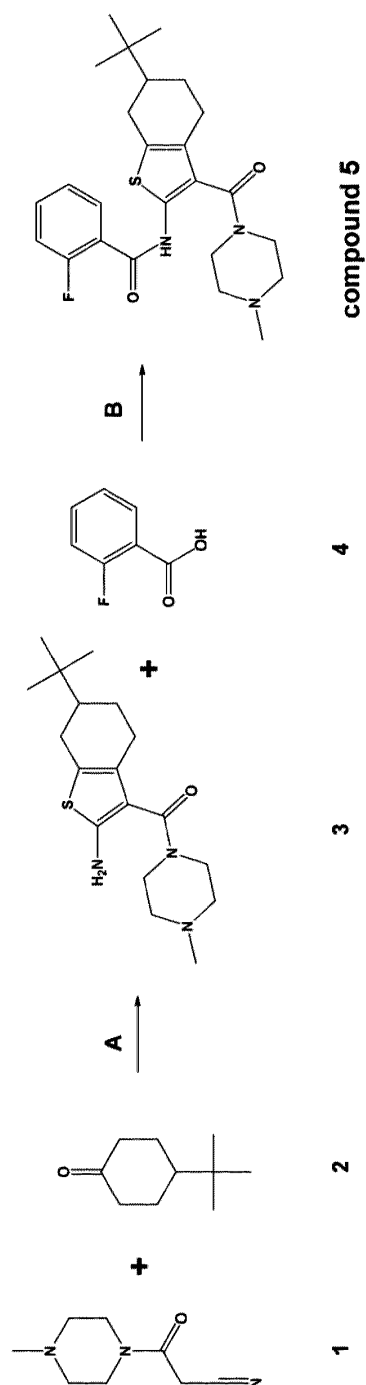


Fig. 12

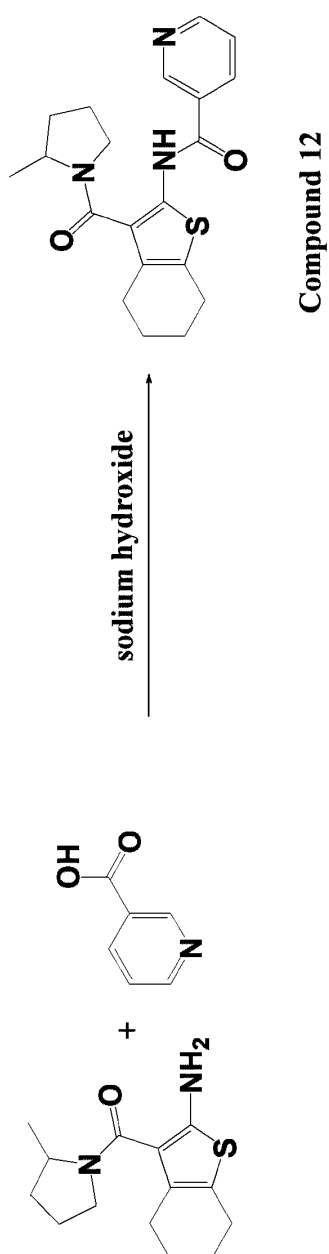
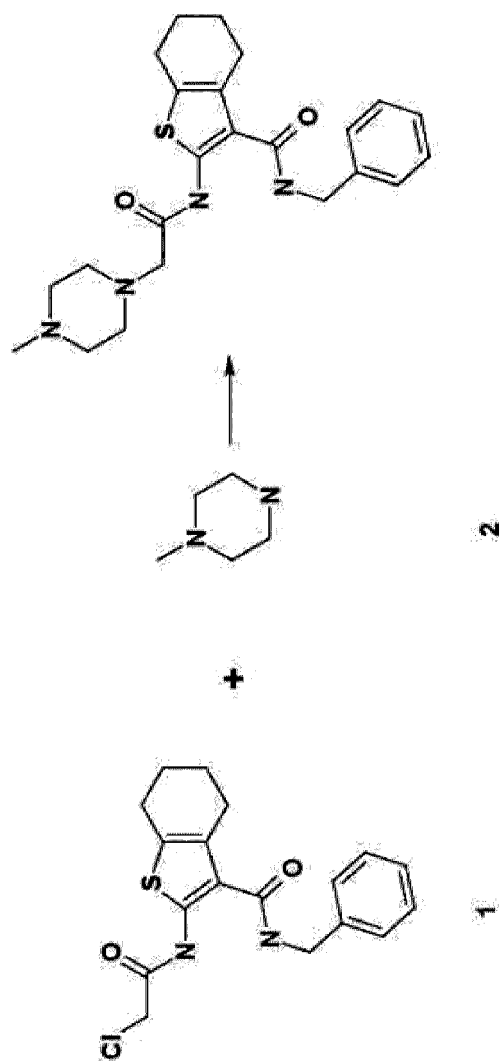


Fig. 13



compound 10

Fig. 14

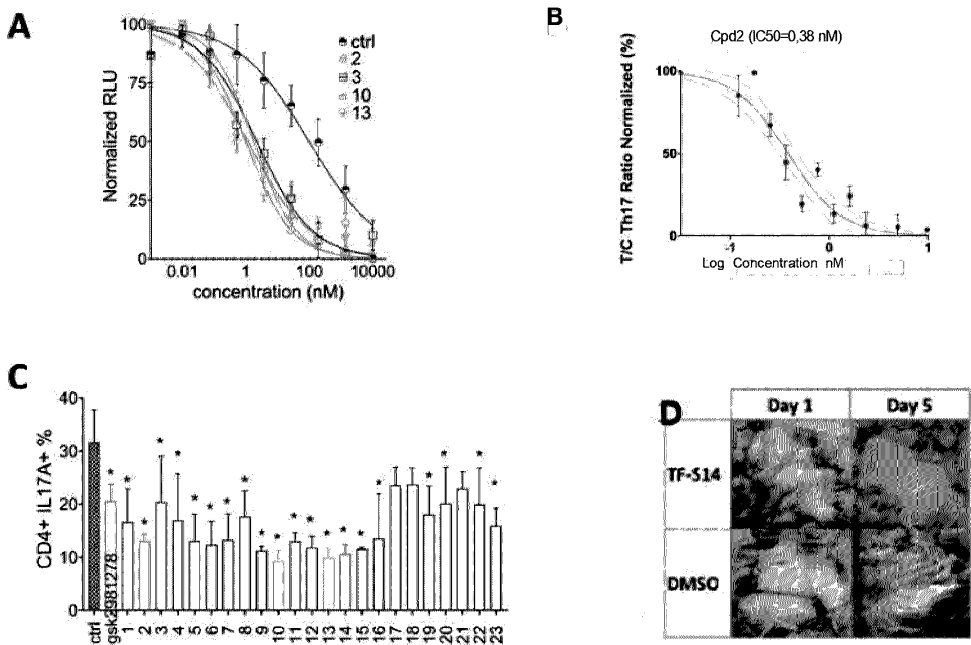


Fig. 15

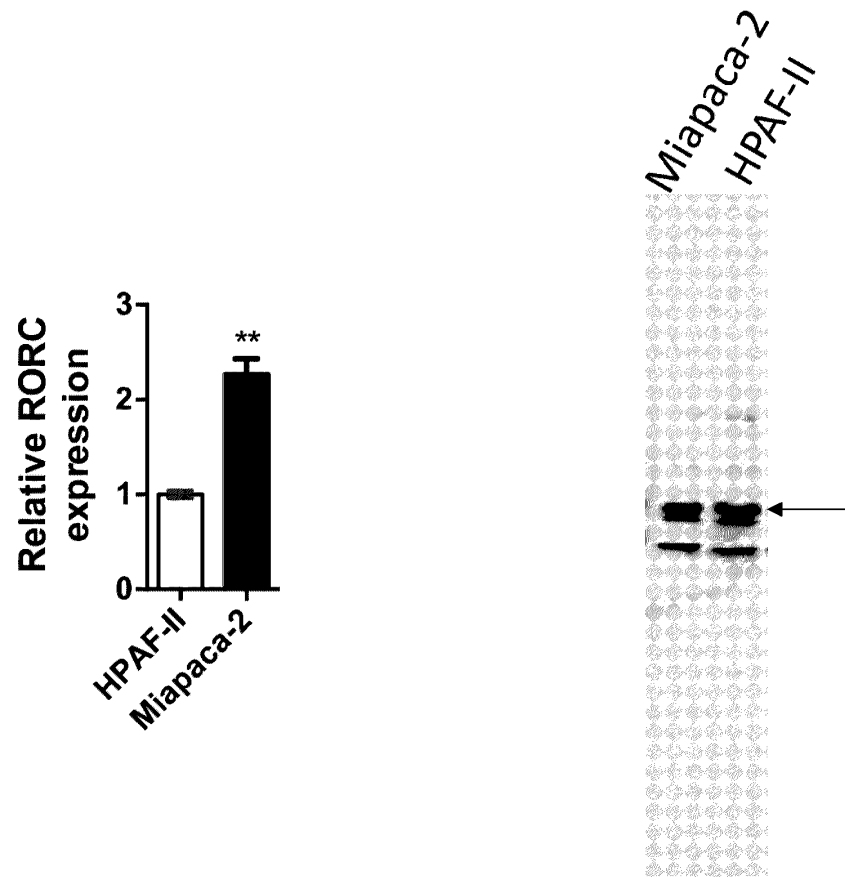


Fig. 16

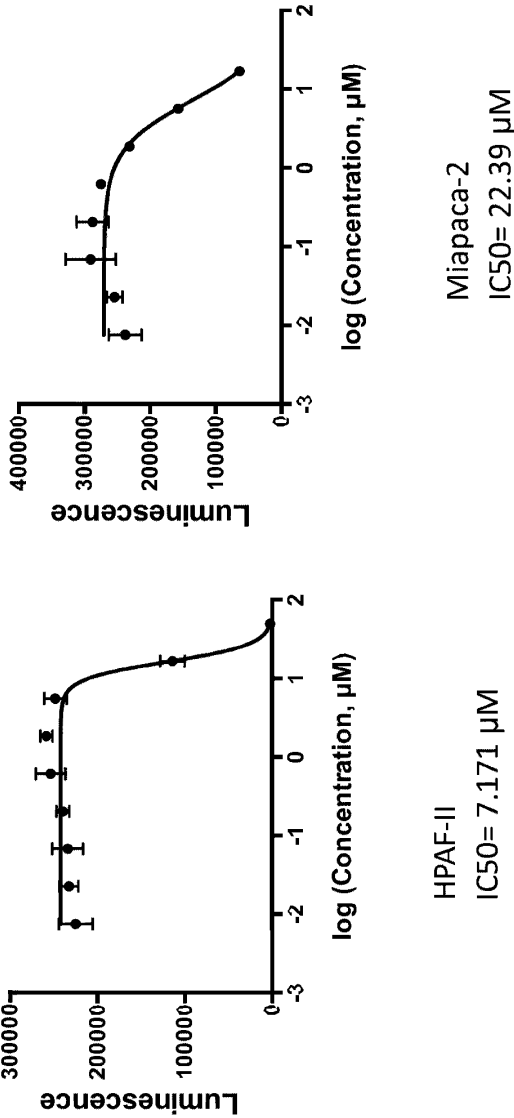


Fig. 17

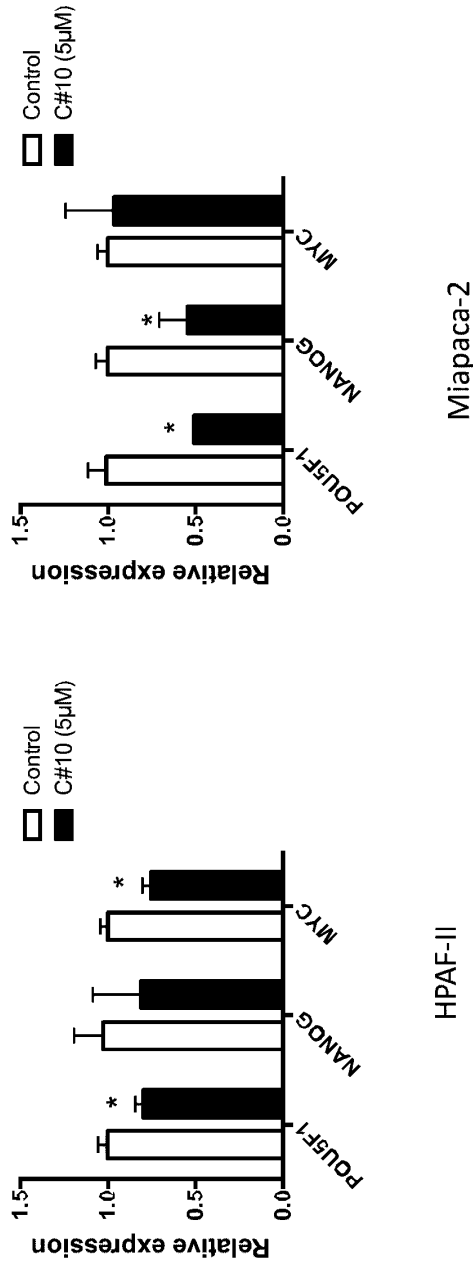


Fig. 18

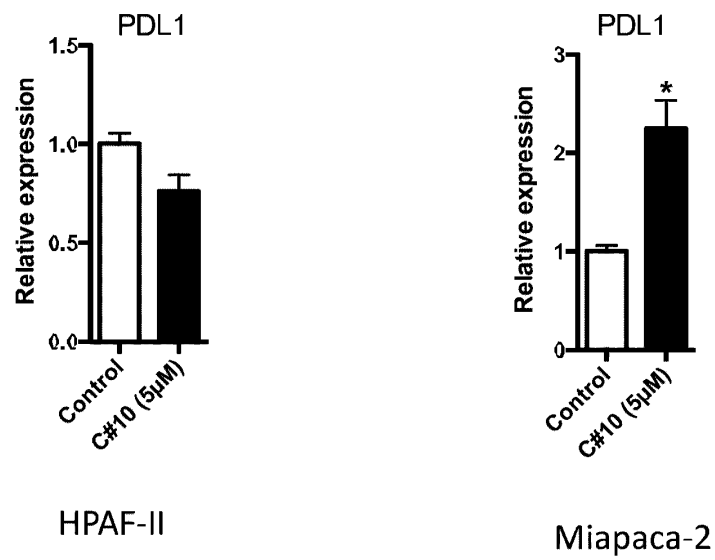
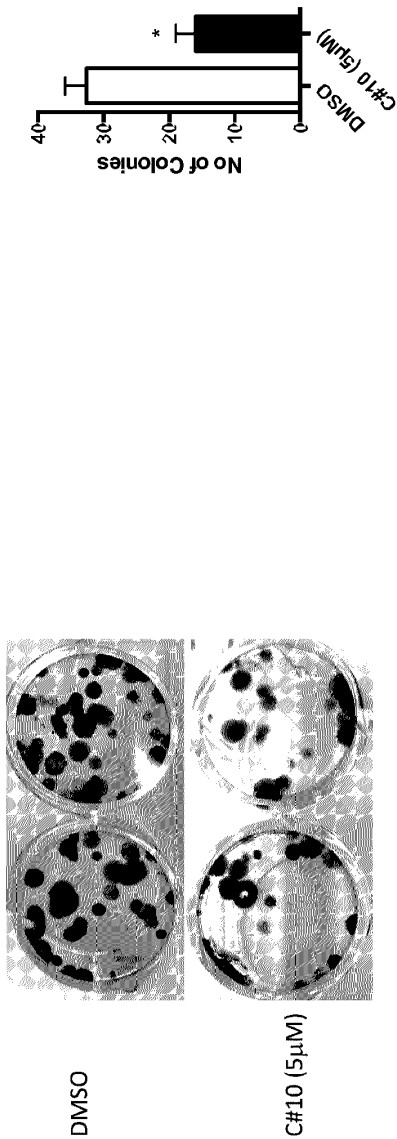


Fig. 19

Colony assay- HPAF-II



Colony assay-Miapaca-2

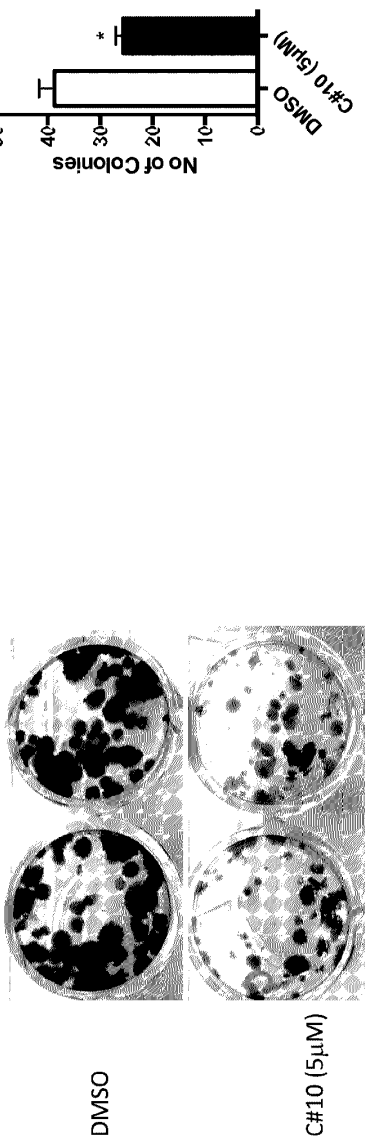


Fig. 20

HPAF-II Pancreatic Cancer Cell Line

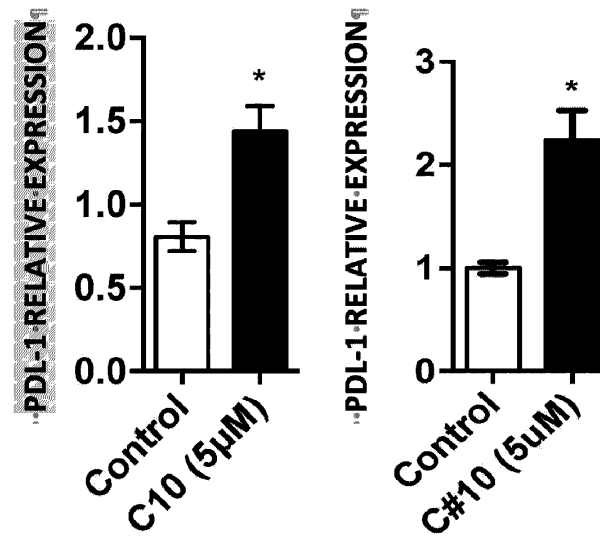
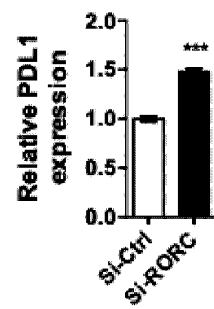
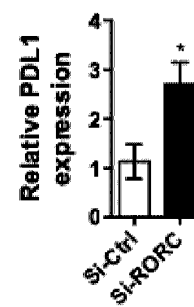


Fig. 21A

Effect of RORC knock down on checkpoint “PDL1” expression

MDA-MB-231



Sum-159

Fig. 21B

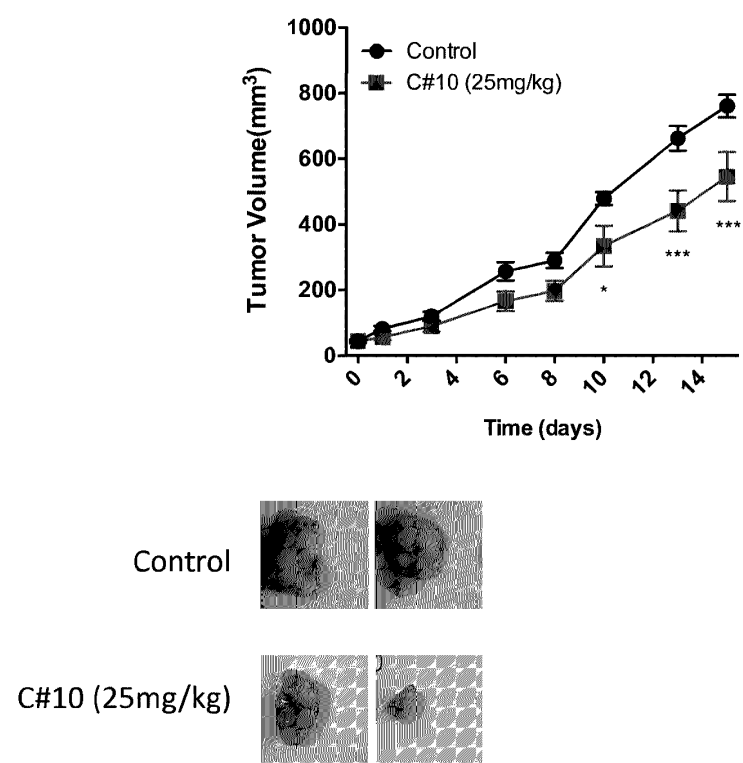


Fig. 22

RORC Expression in breast cancer cell lines

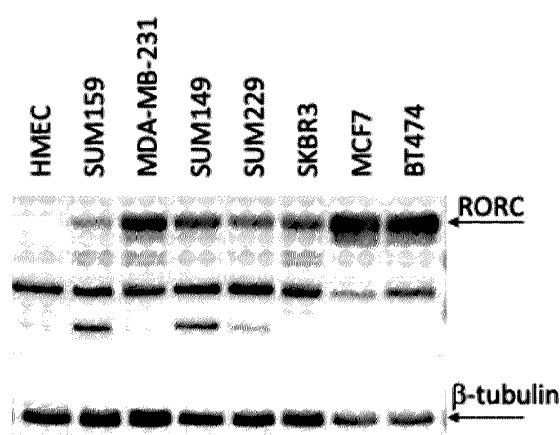


Fig. 23A

RORC Expression in TNBC cell lines

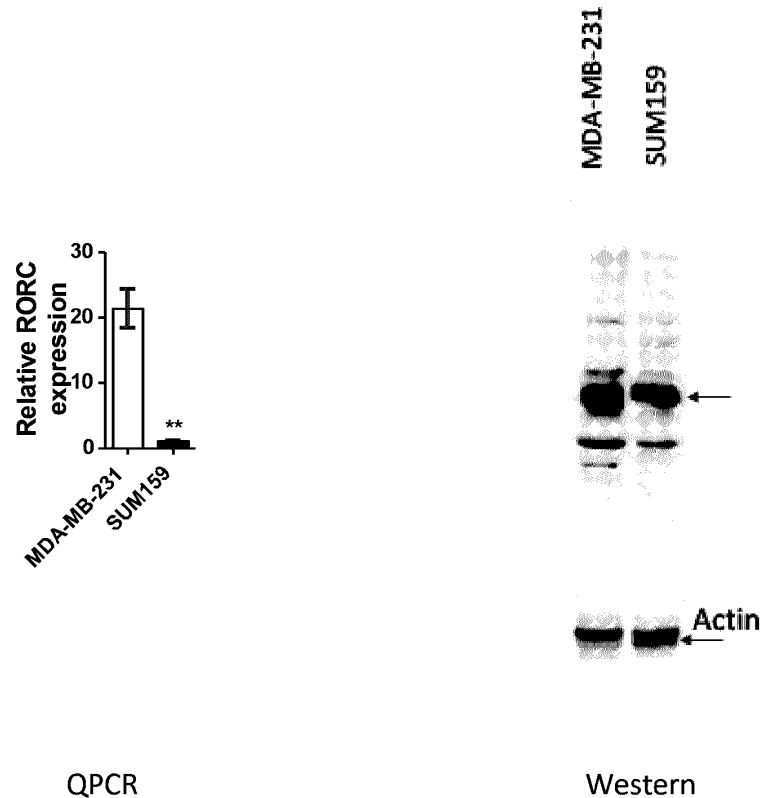


Fig. 23B

IC50 for C#10 (Cell titer glo assay)

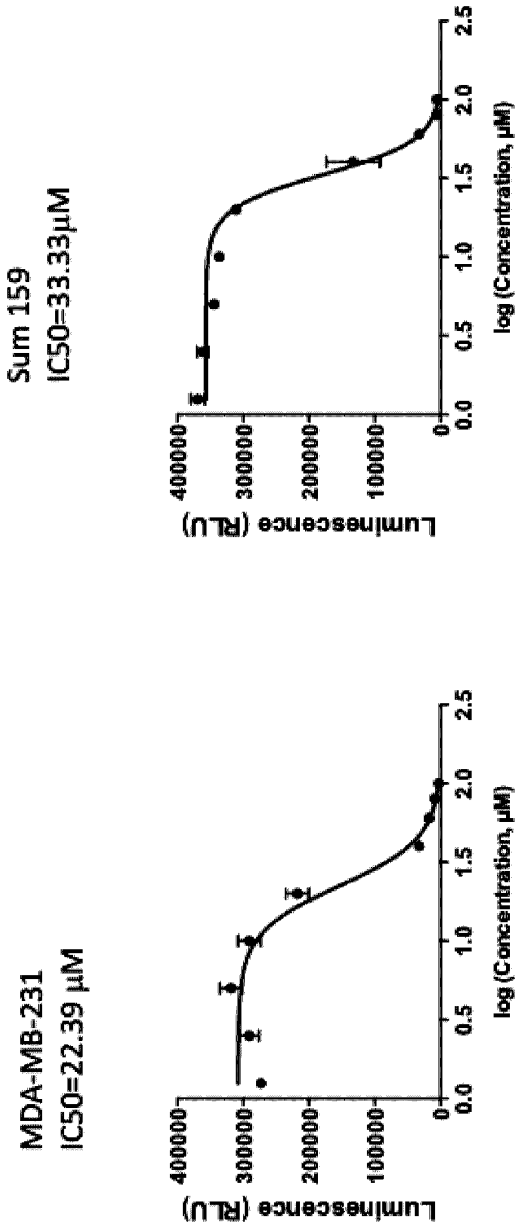
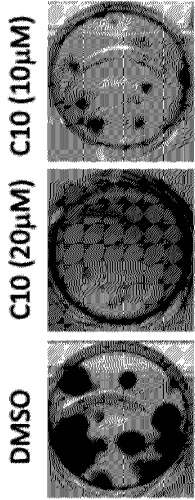


Fig. 24

Effect of C#10 on colony formation

MDA-MB-231



Sum-159

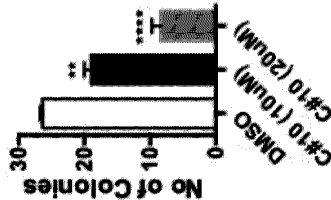
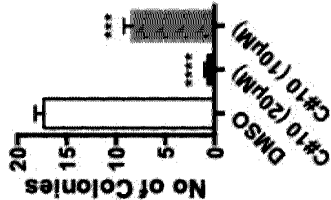
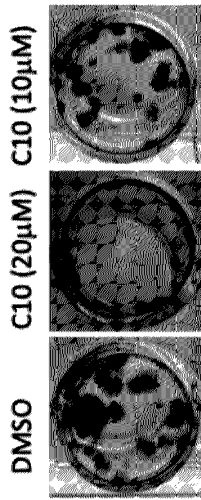


Fig. 25

Effect of C10 on tumor volume in breast cancer mouse model

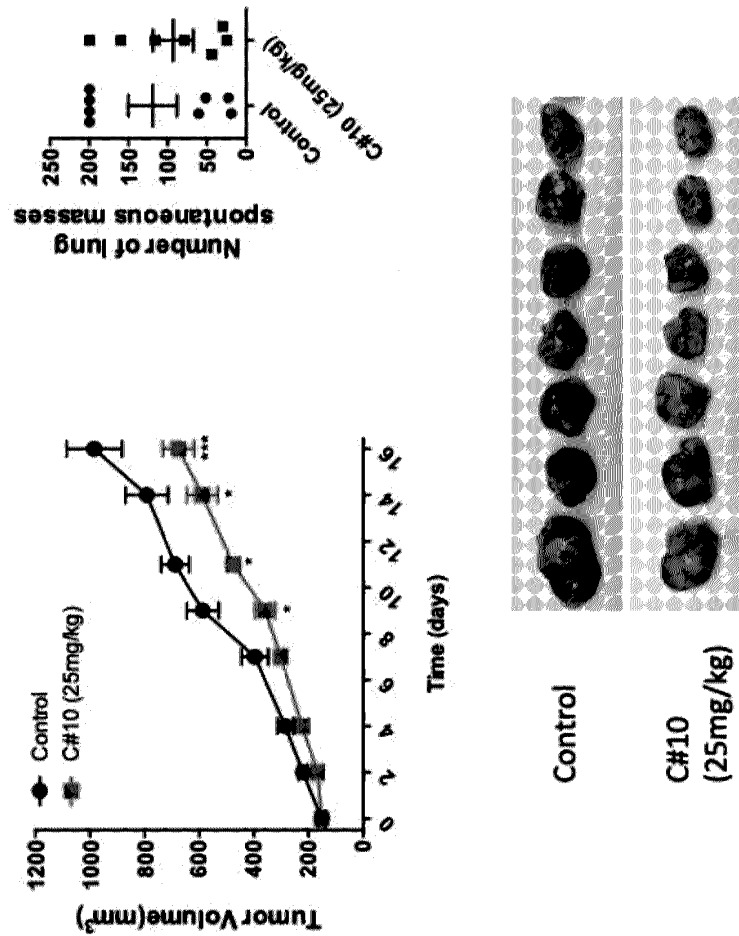


Fig. 26

Effect of RORC knock down on cell survival

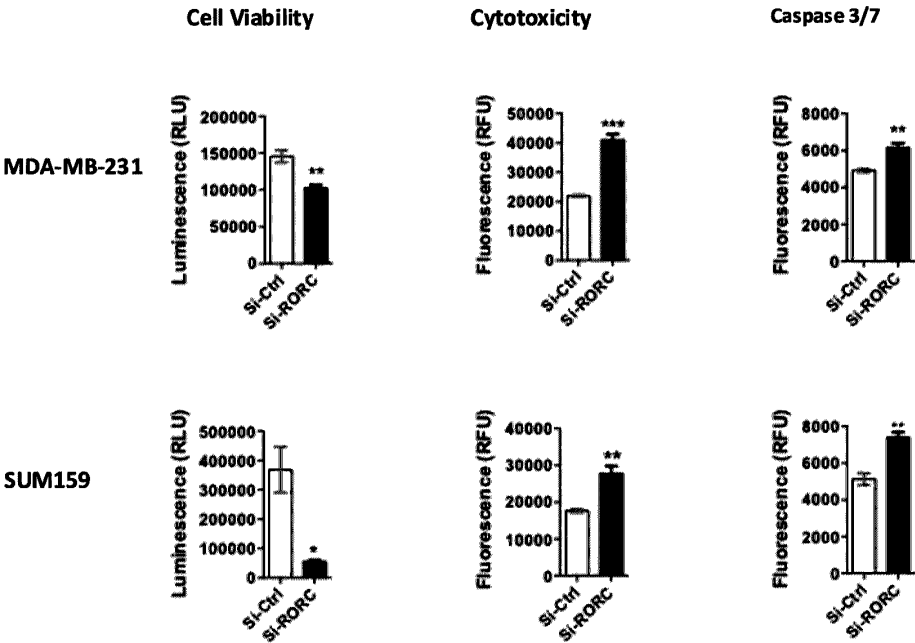


Fig. 27

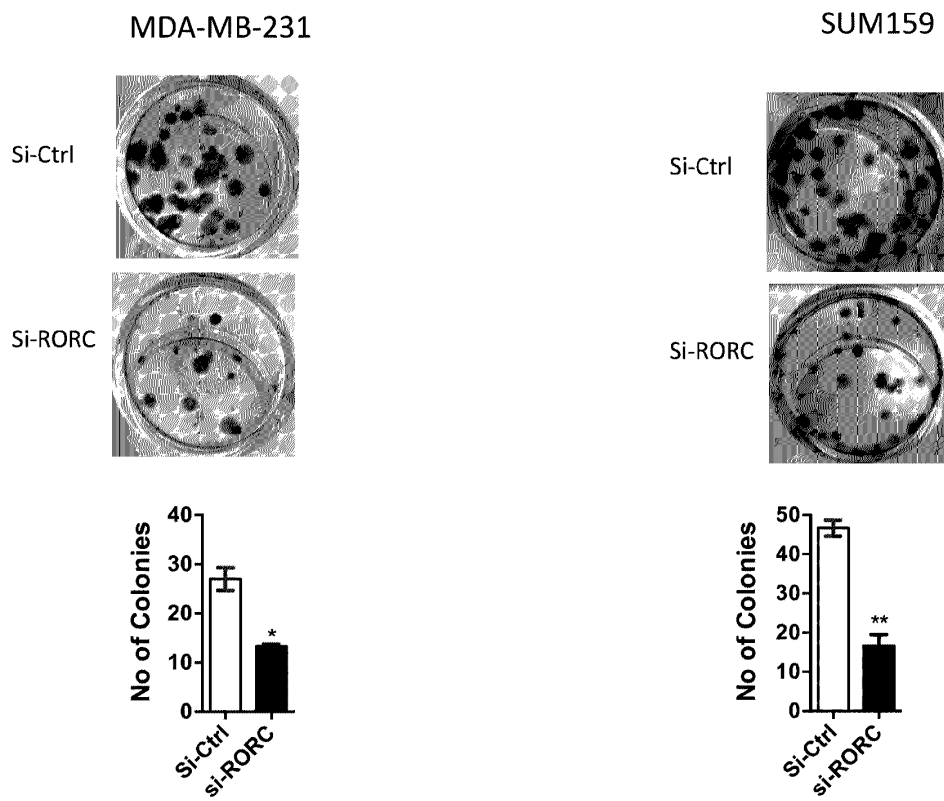


Fig. 28



Fig. 29

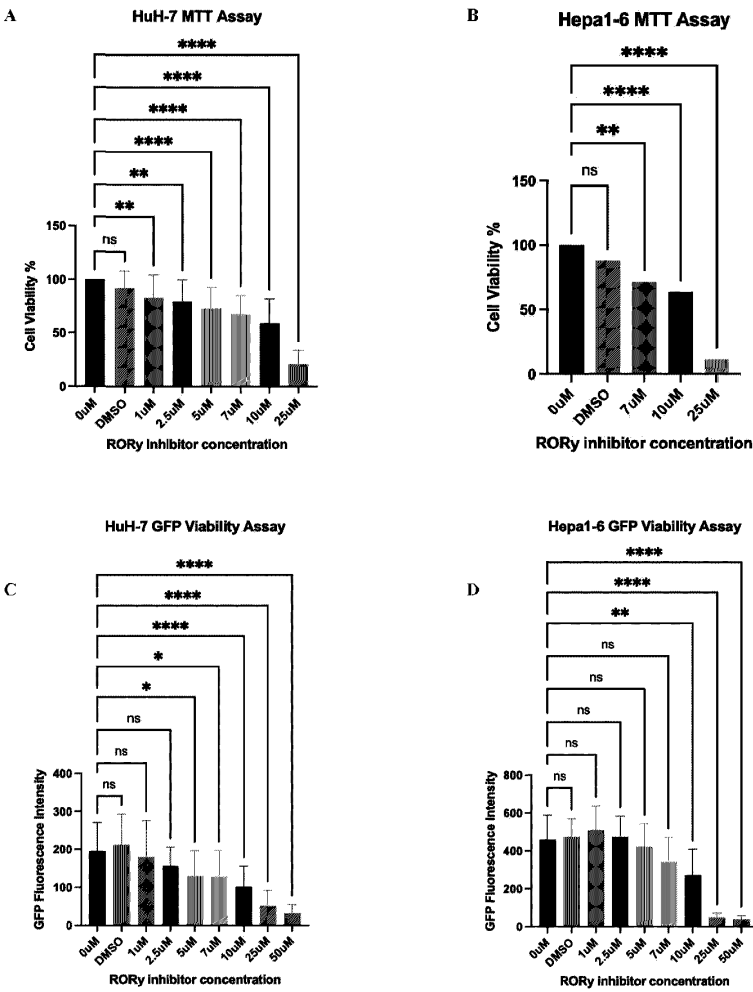


Fig. 30

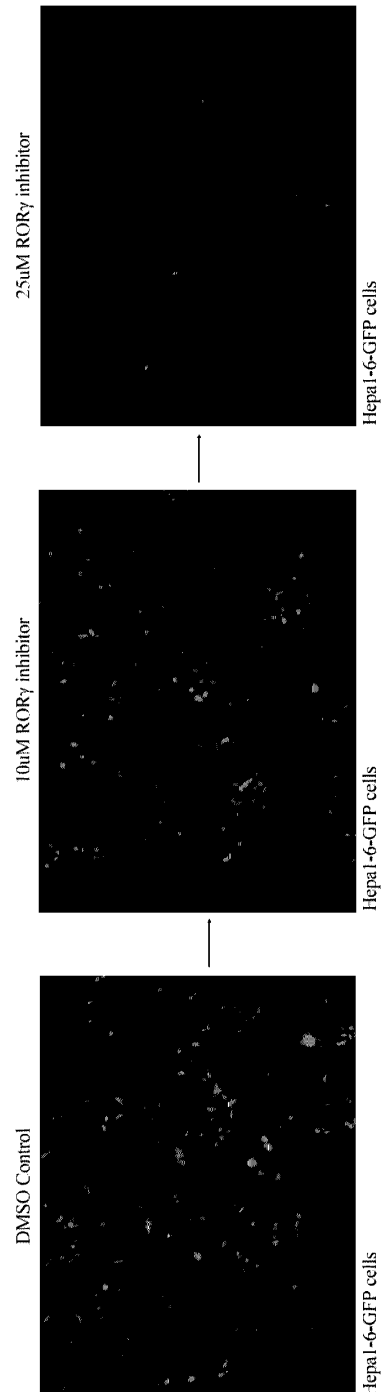


Fig. 31

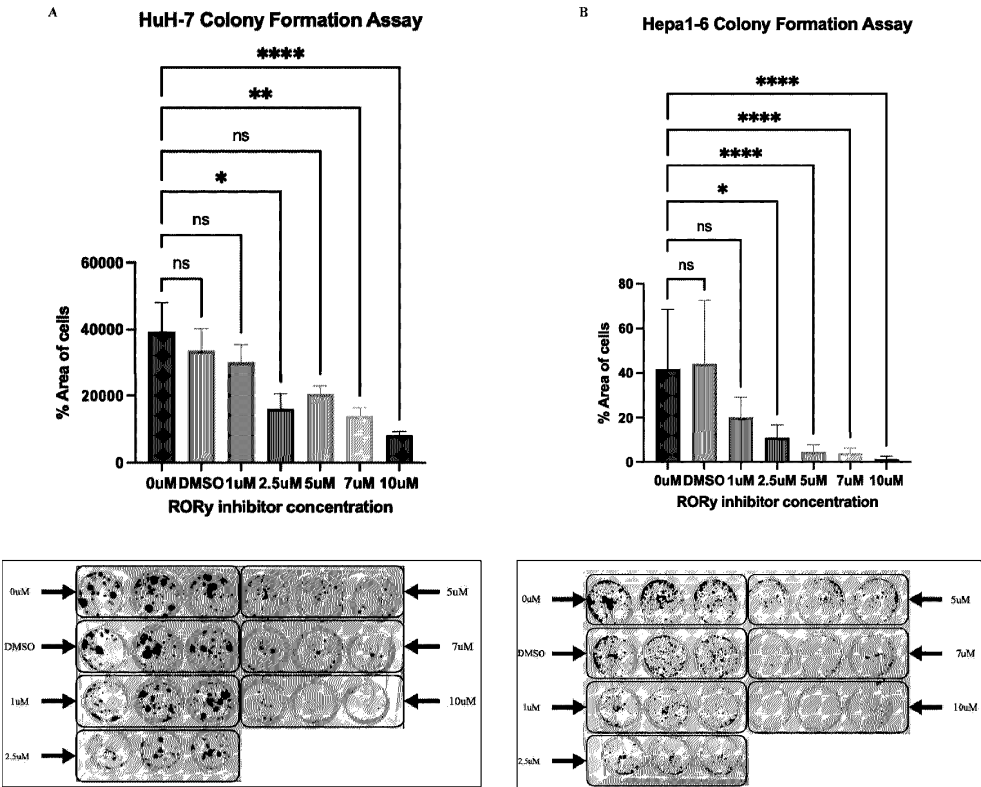


Fig. 32

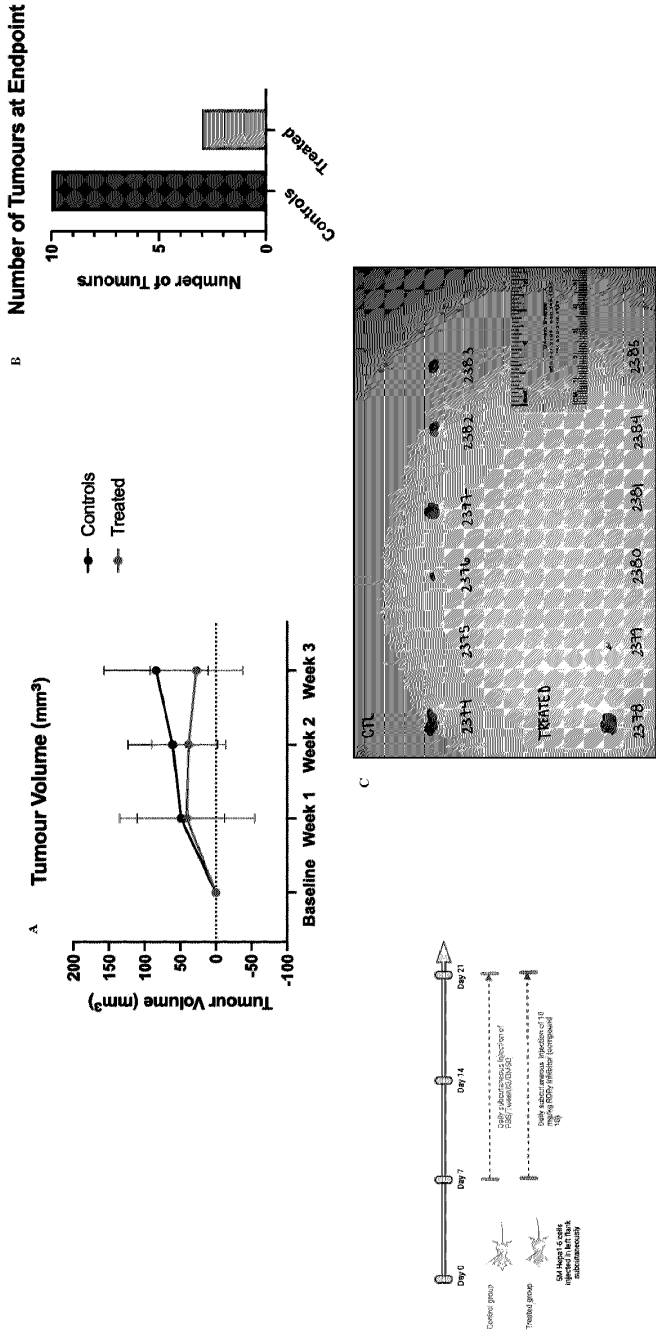


Fig. 33

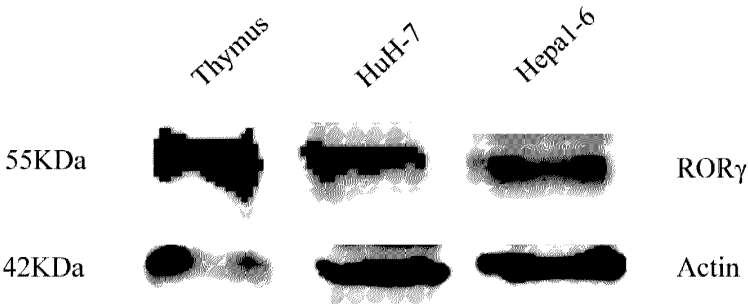
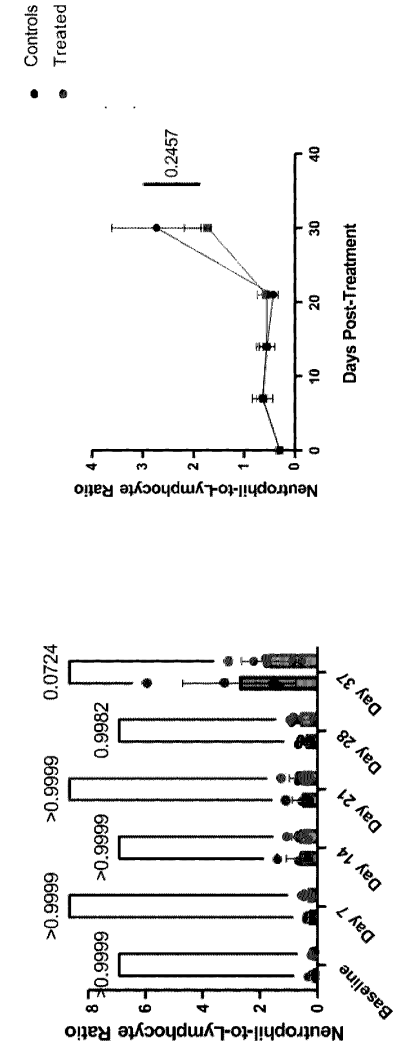


Fig. 34

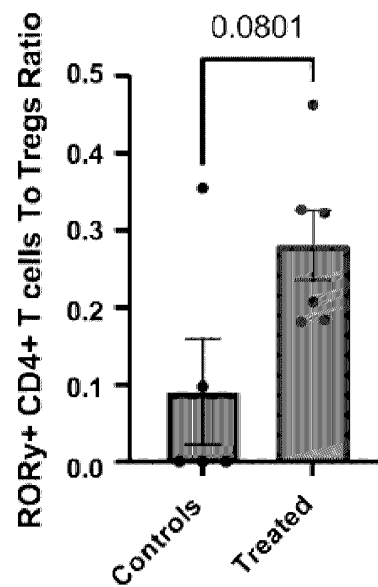
Circulating NLR



No significant difference in circulating NLR between control and treated, but there is a trend towards reduced circulating NLR in treated group.

Fig. 35

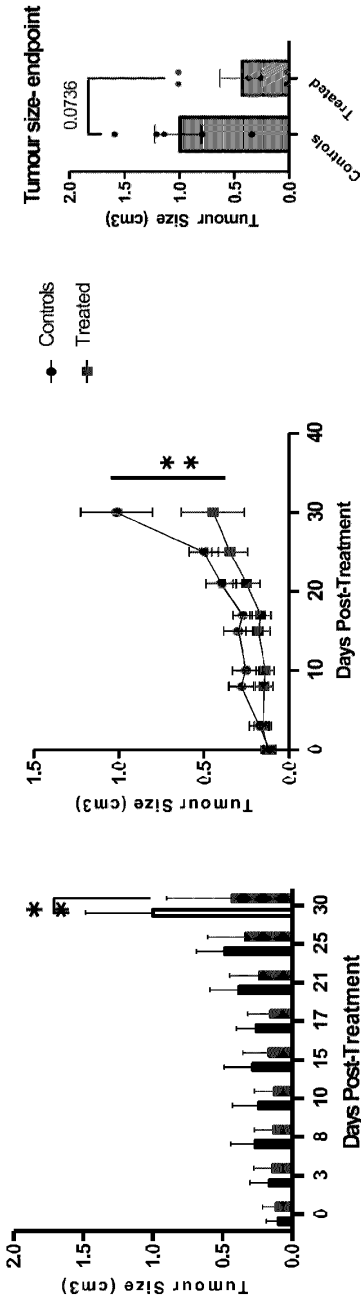
Circulating Th17/Tregs Ratio



Interesting trend : Shift away from an immunosuppressive environment

Fig. 36

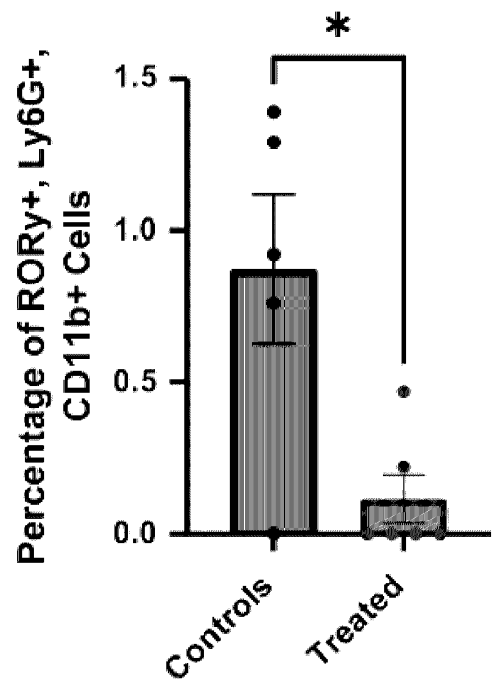
RORy Inhibition Slows Cancer Progression



Significant decrease in tumour growth rate in treated group compared to control group. We know that the RORy inhibitor is affecting cancer progression

Fig. 37

RORy Inhibition Reduces Intratumoural
Infiltration of RORy+ Neutrophils



Significant reduction in intratumoural RORy+ neutrophils in treated group compared to control group.

Fig. 38

RORγ Inhibition Favours a Less
Immunosuppressive Environment

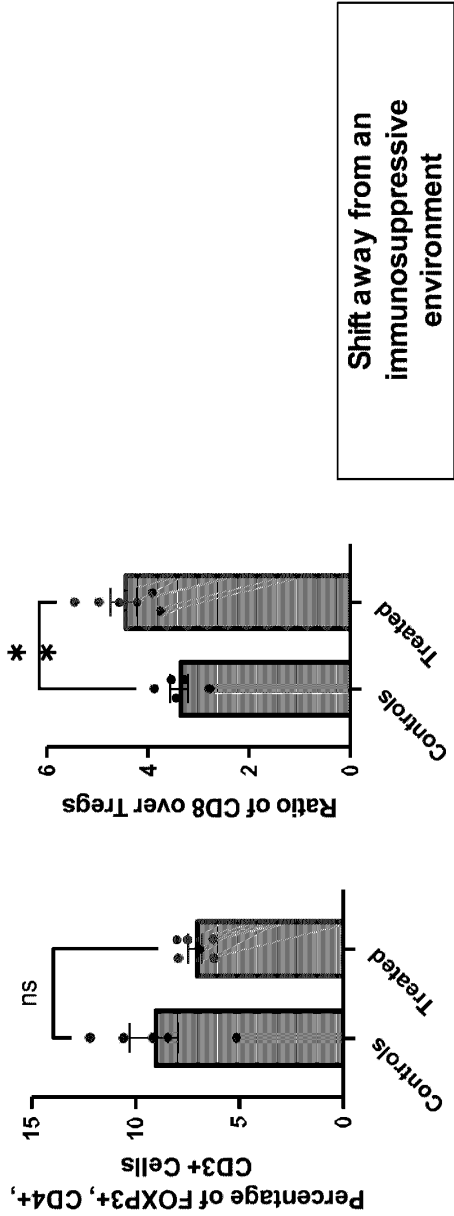


Fig. 39

RORy Inhibition Favours a Less
Immunosuppressive Environment

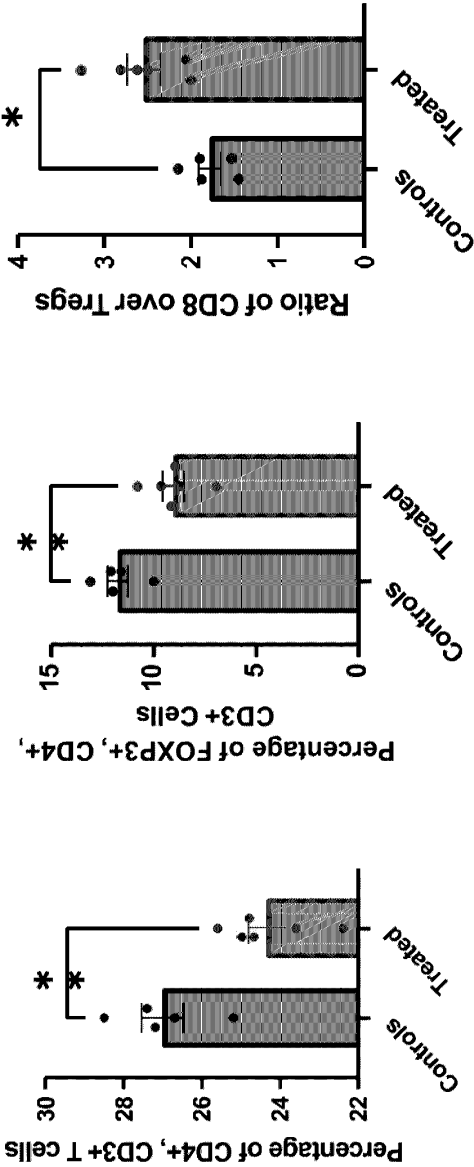


Fig. 40

Similar Conclusions for Lower
Dose Treatment (5mg/kg)

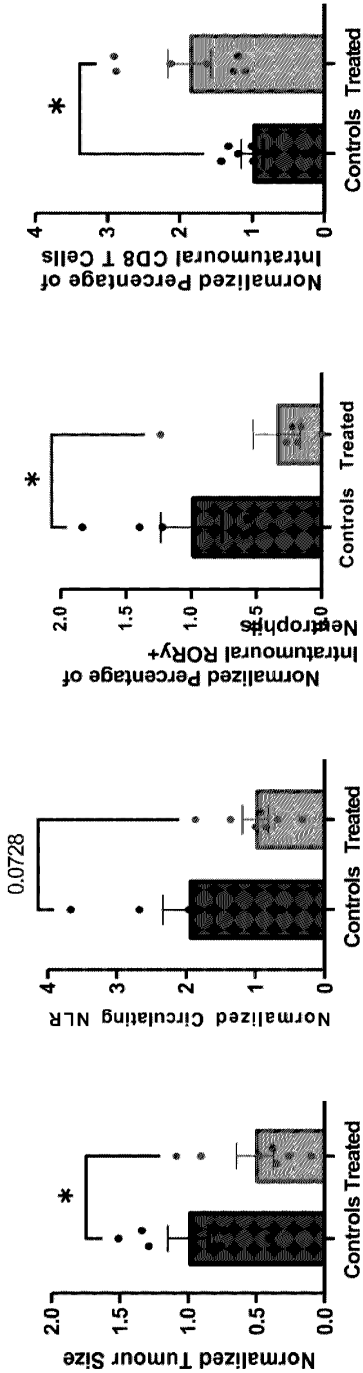
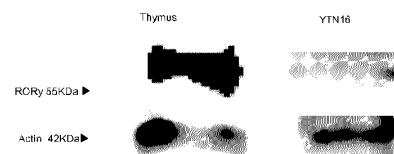


Fig. 41

RORy Expression in YTN16-GFP

- ▶ Flow cytometry
 - ▶ Mean of 2.57% of YTN16 cells expressing RORy
- ▶ WB
 - ▶ Concur that it is a low-RORy expressing cell line
 - ▶ Still trying to get the WB working with monensin-treated YTN16-GFP



Collaborative work with S. Leo

Fig. 42

Assessment of Circulating RORy+ Neutrophils in GEA Patients

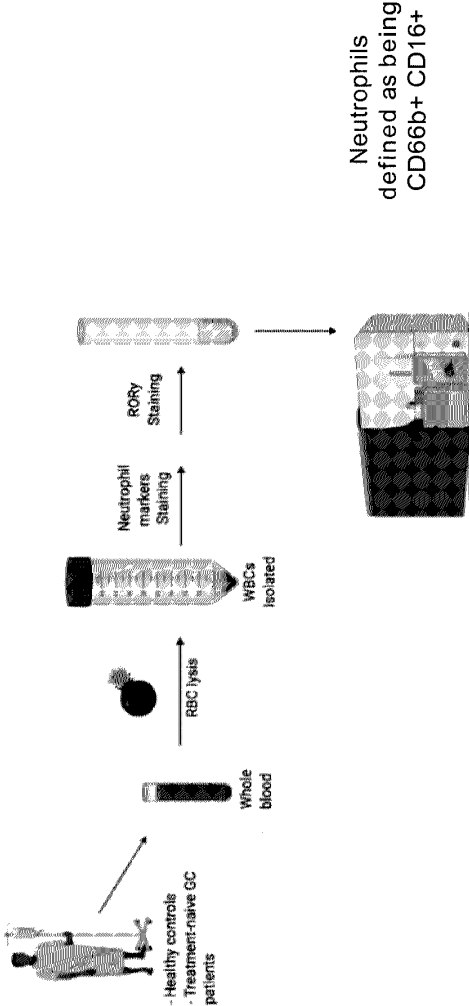


Fig. 43

Significant Increase in Circulating RORγ+ Neutrophils Prevalence in High NLR GEA Patients

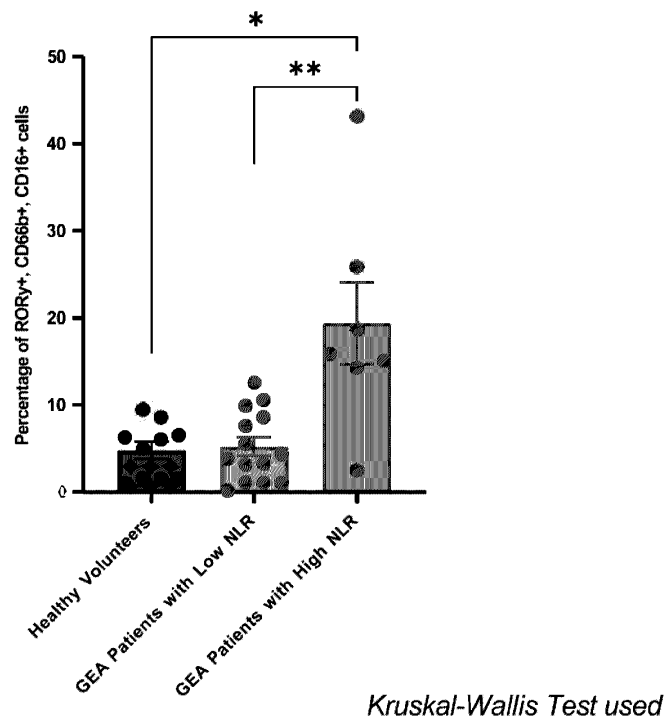
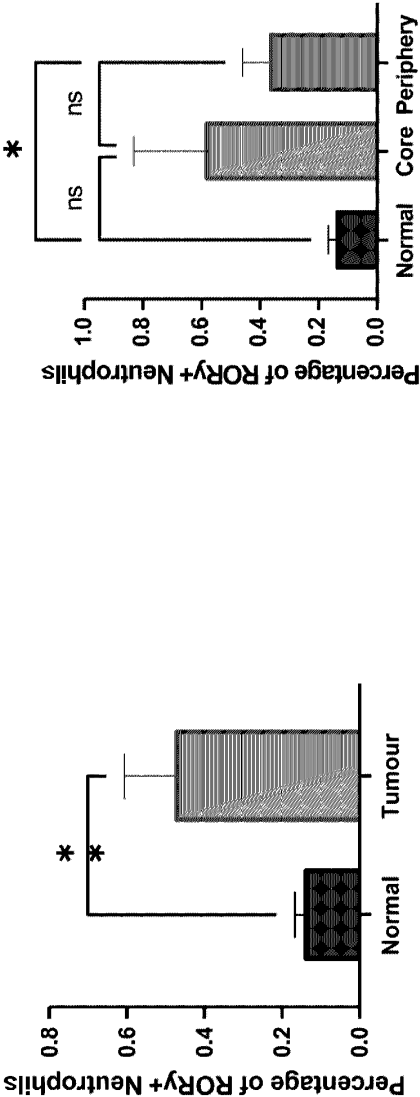


Fig. 44

RORy+ Neutrophils Migrate to Tumour



▲ Increased prevalence of RORy+ neutrophils (RORy+ Arg1+ cells) in tumour tissues, more specifically in tumour periphery

Fig. 45

RORy+ Neutrophils show a trend to reduced patient survival

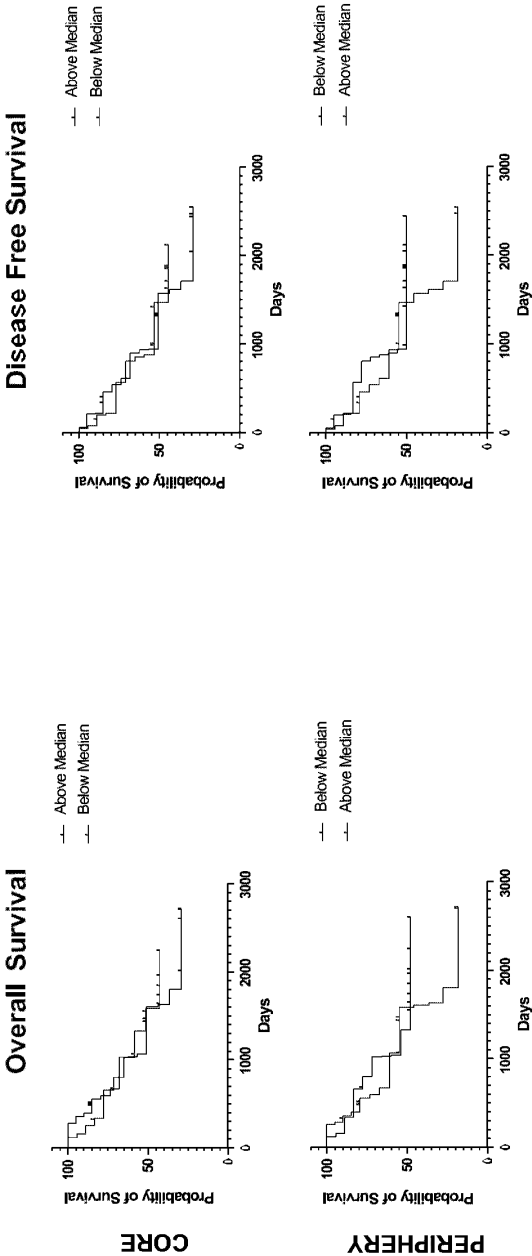
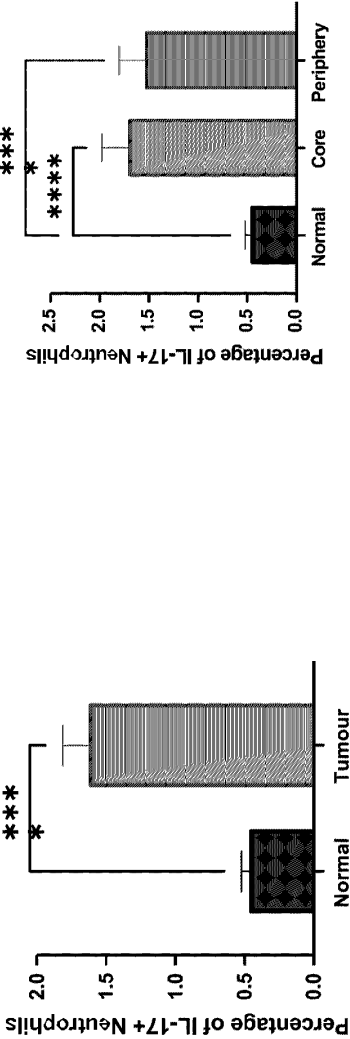


Fig. 46

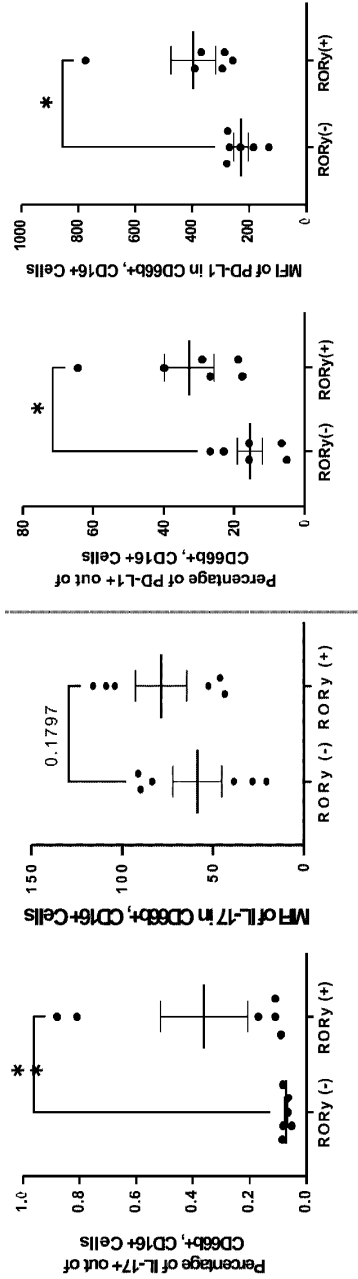
IL-17+ Neutrophils Migrate to Tumour



- ▲ Increased IL-17+ Arg-1+ cells (IL-17+ neutrophils) infiltration in cancerous tissues
- ▲ Not able to quantify this subset of neutrophils within the circulation
- ▲ No effect on OS and DFS

Fig. 47

Increased Expression of IL-17 and PD-L1 in RORγ+ Neutrophils



- ▲ IL-17 = pro-inflammatory cytokine with RORγ as its master transcriptional regulator
- ▲ PD-L1-expressing neutrophils are **considered pro-tumor** as they are able to suppress cytotoxic T cells and are propagated with disease progression.

Fig. 48

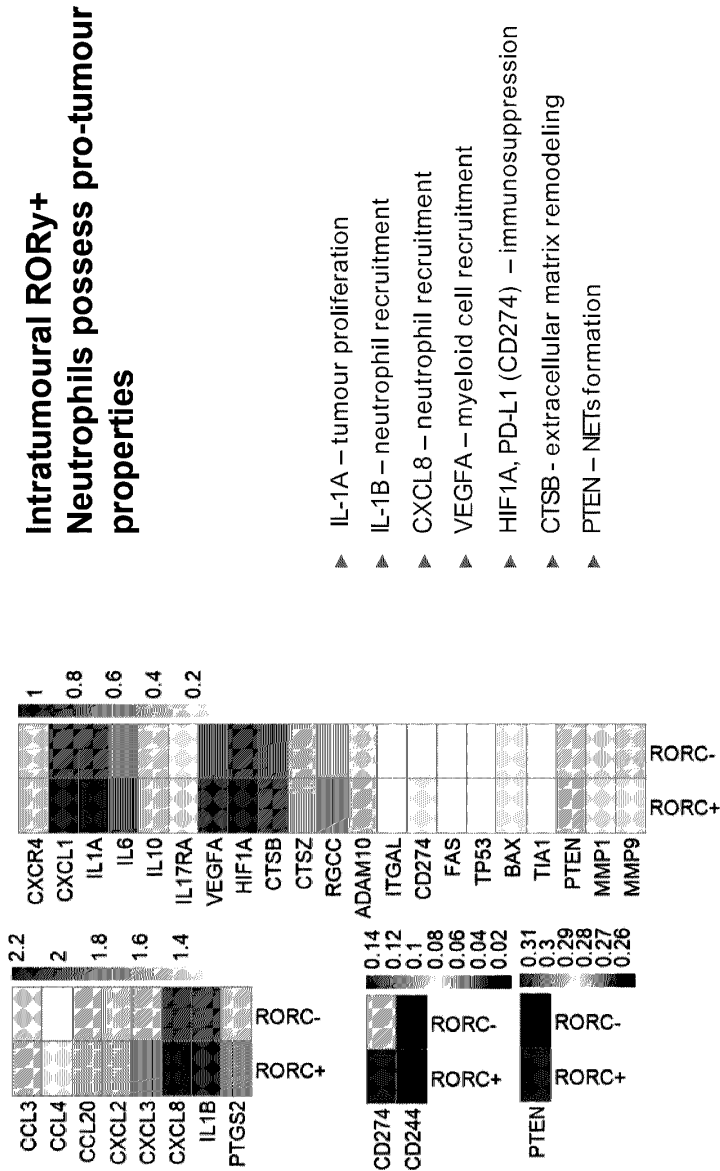


Fig. 49

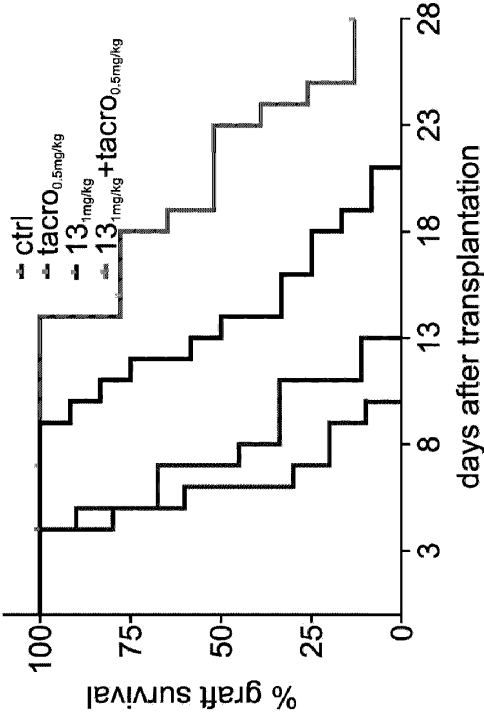


Fig. 50

Pathway Enrichment Analysis
GSEA (Hallmark)

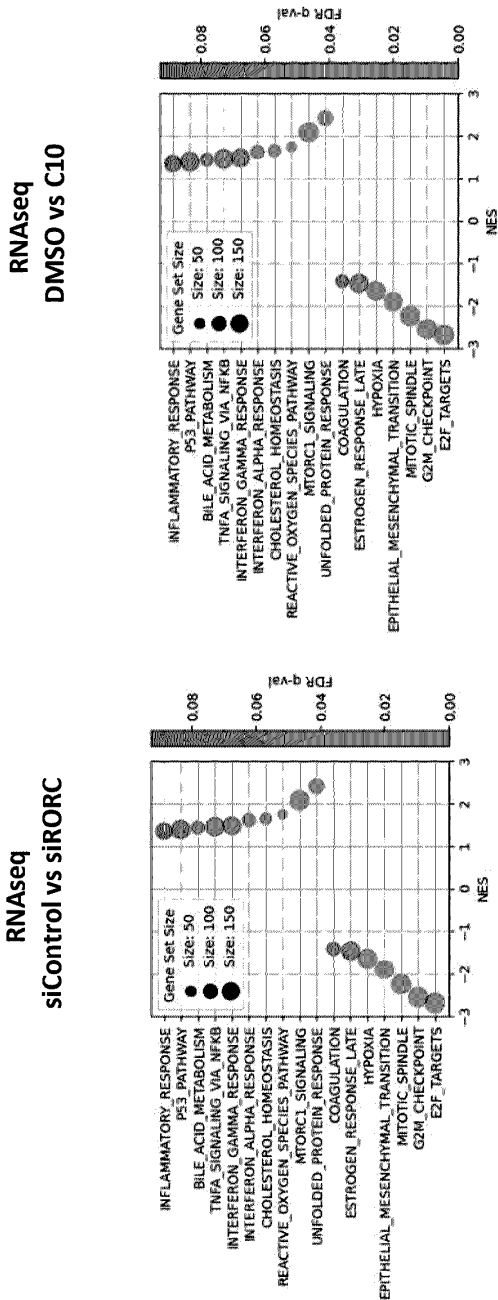


Fig. 51

Pathway Enrichment Analysis
GSEA (Hallmark)

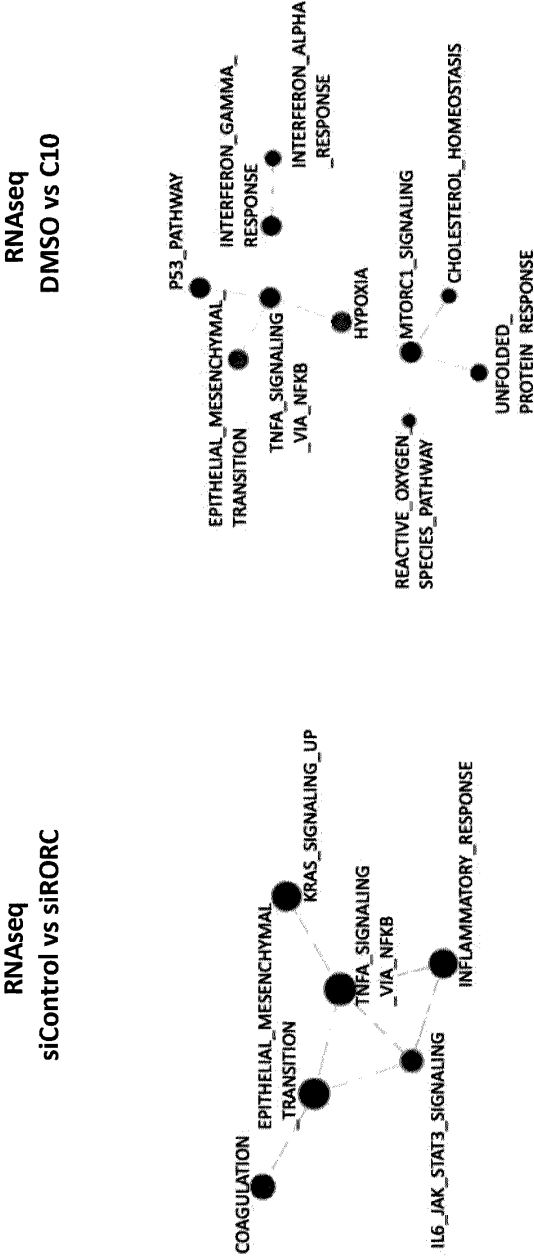


Fig. 52

Pathway Enrichment Analysis
GSEA (KEGG)

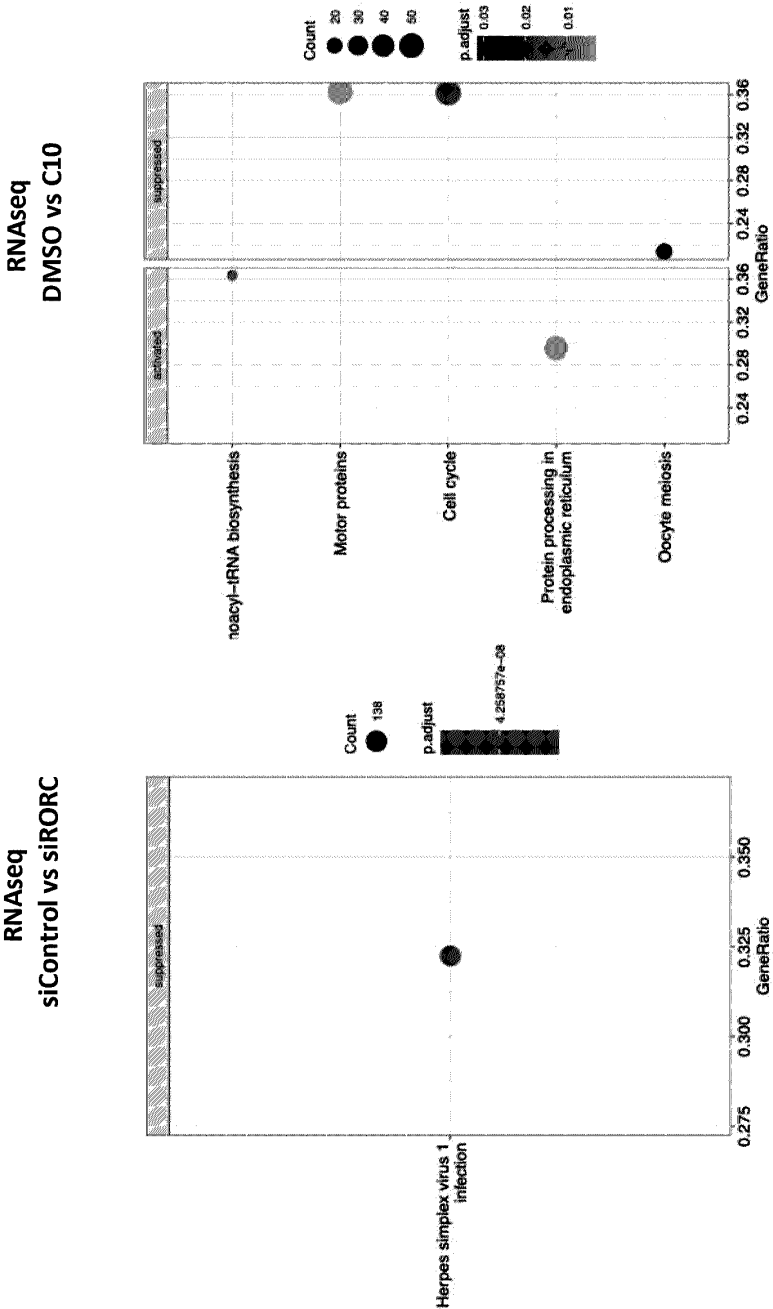


Fig. 54

Pathway Enrichment Analysis
GSEA (Reactome)

RNAseq
siControl vs siRORC

RNAseq
DMSO vs C10

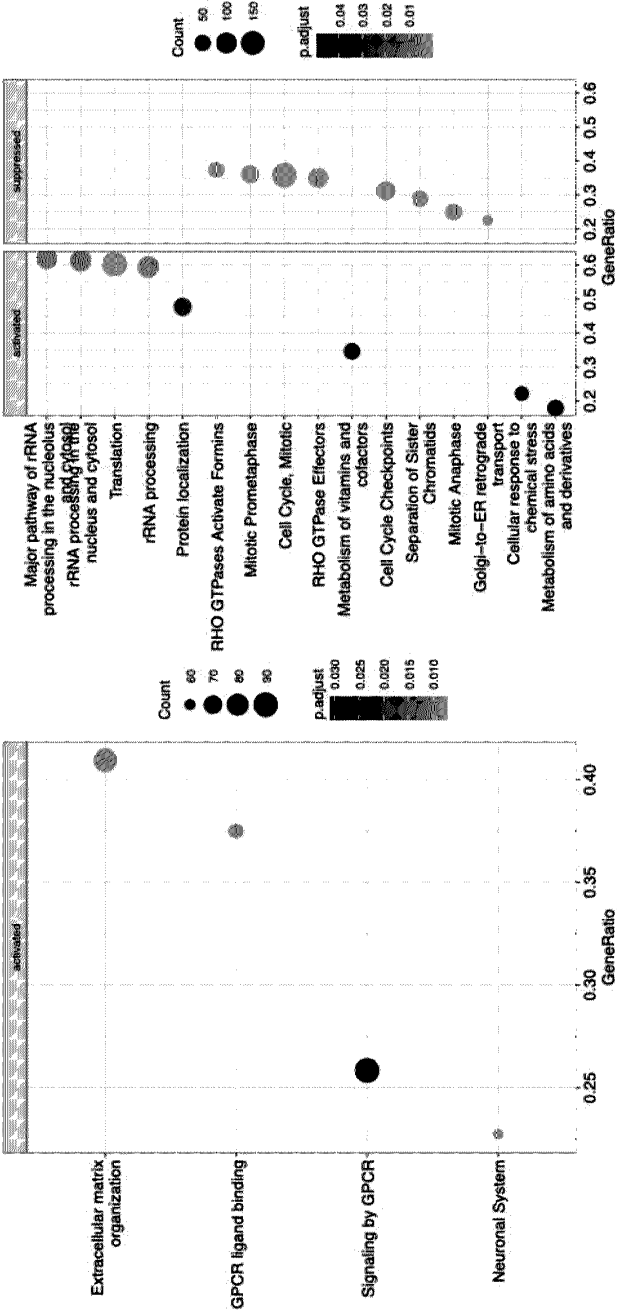


Fig. 55