Supplement figures:

Figure S1: HDAC-I/II and GSK-3β inhibitors significantly decrease pancreatic cancer cell survival and EMT.

(A) Expression of GSK-3β in normal and PDAC tissues from KPC mice. (B) Protein levels of HDAC4, HDAC7, p-HDAC7 and histone acetylation in tissues of B6 and KPC mice were measured by Western. MIA PaCa-2 Cells were cultured for 72h in the presence or absence of 1μM of GSK-3β inhibitor Tideglusib or HDAC-I/II inhibitor Saha. Cell survival was measured by MTT assay (C). Cells were transfected with GSK-3β siRNA or scrambled siRNA (E). Protein levels of Twist, Snail1 and Vimentin were measured by Western blot (D, E). Blots were re-probed for GAPDH to confirm equal loading (B, D, E). &, $p < 0.05$ *versus* Tideglusib alone.

Figure S2: Synthesis steps of Metavert and structure of Metavert analogs.

(A) Synthesis steps of Metavert. Structure of Metavert analogs CSME-188543 (B) and CSME-185643 (C). (D) MIA PaCa-2 cells were treated with indicated concentrations of CSME-188543 or CSME-185643 for 72h and cell survival was measured by MTT assay. *: Lowest concentration at which significance is achieved. *, $p < 0.05$ *versus* control.

Figure S3: Metavert decreases the level of phosphorylated STAT3 and p65 and increases β-catenin.

BxPC-3 cells were cultured in the presence of indicated doses of Metavert for 72h. Protein levels of p-STAT3 and p-p65 (A) and β-catenin (B) were measured by Western blot. Blots were re-probed for GAPDH to confirm equal loading.

Figure S4: Metavert affects its expected targets in mice with no apparent toxicity to vital organs.

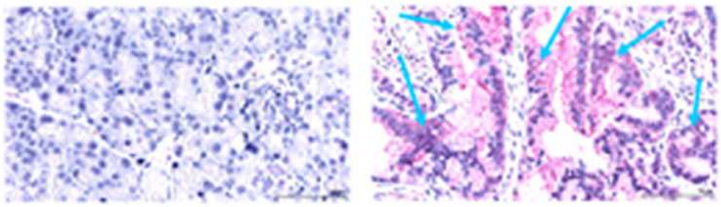
(A) Protein levels of histone acetylation (H3K9) and GSK-3β serine 9 phosphorylation were measured by Western in the lysates of pancreatic tissues. Blots were re-probed for total Erk to confirm equal loading. (B) Average weight of KPC mice from the age of 2 months until death. (C) Activities of LDH, AST, Alkaline phosphatase, and Creatinine in the blood of KPC mice. (D) Pictures of control and Metavert -treated KPC mice showing the abdomen. Red arrows show the pancreas with cancer. (E, F) H&E staining and S100P staining, respectively, of pancreatic tissues (*a* and *c*: 4x; *b* and *d*: 10x).

Figure S5: Metavert improves survival and prevents metastasis in a syngeneic mouse model of pancreatic cancer.

Mouse UN-KPC961-Luc cancer cells were injected in the pancreas of B6.129 mice at the age of 2 months and treatment with Metavert (5mg/Kg) or vehicle 3 times per week started until sacrifice or death (set 1) or for 4 weeks (set 2). (A) Imaging of mice 3 weeks after start of Metavert/vehicle treatment (set 1). (B) Survival curve of the syngeneic mice (set 1). (C) Imaging of the pancreas of mice sacrificed 4 weeks after start of treatment (set 2 of mice). (D) pictures showing presence of liver metastasis in control syngeneic mice compared to no metastasis in Metavert-treated mice (set 2 of mice).

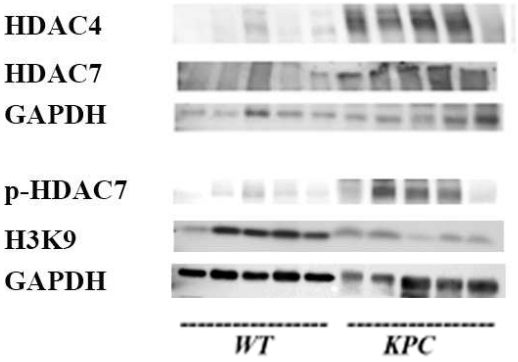
Figure S6: Scheme of the glucose metabolic pathways affected by Metavert.

A

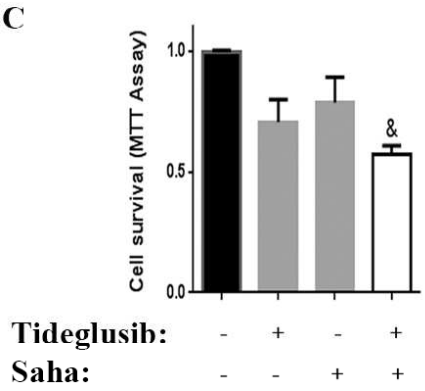


Normal pancreas *PDAC*

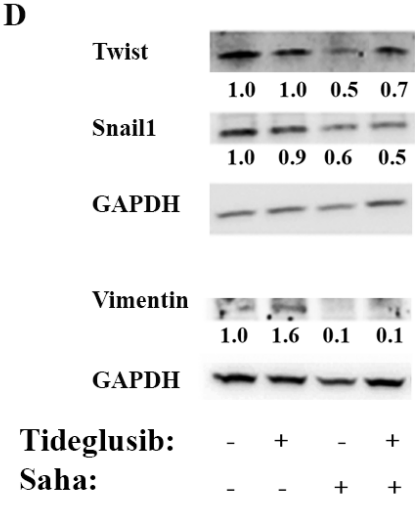
B



C



D



E

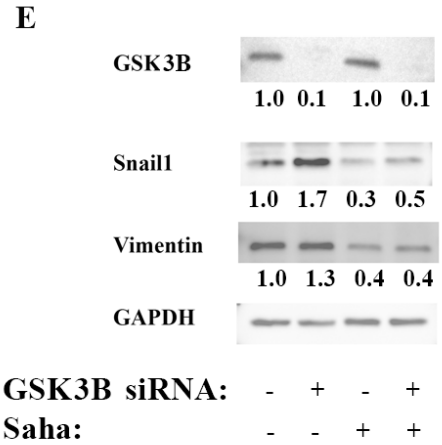
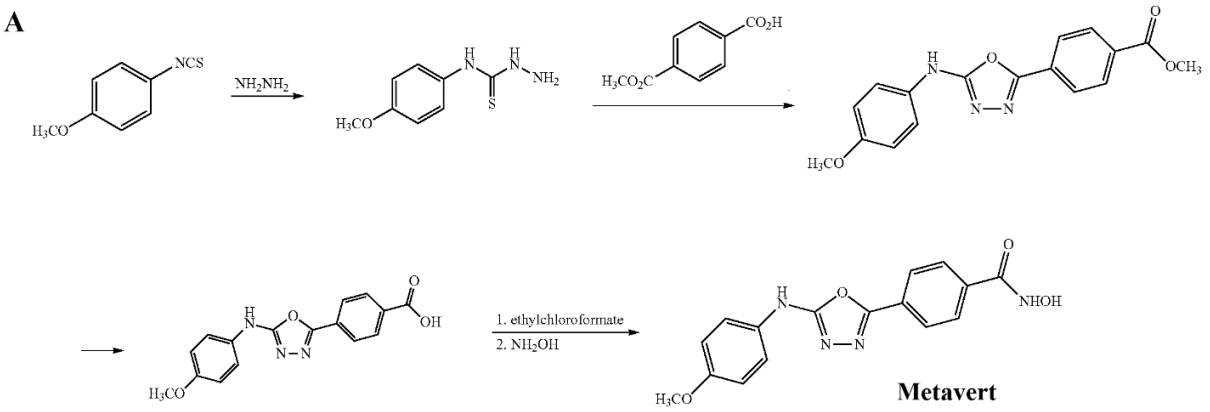
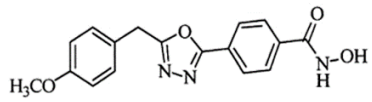
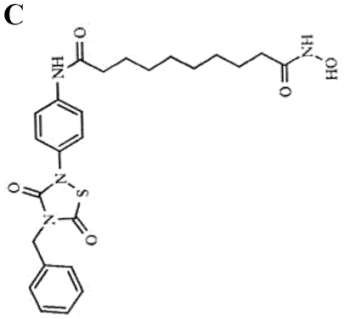


Fig S1


A
NCS
NH_2NH_2
H_3CO
CO_2H
H_3CO_2C
OCH_3
OH
1. ethylchloroformate
2. NH_2OH
NHOH
Metavert


B
H_3CO
N-OH
H


C
NH
HO

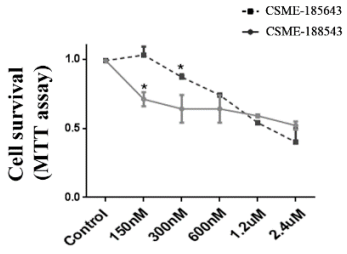

D
CSME-185643
CSME-188543
Cell survival
(MTT assay)
1.0
0.5
0.0
Control
150nM
300nM
600nM
1.2uM
2.4uM

Fig S2

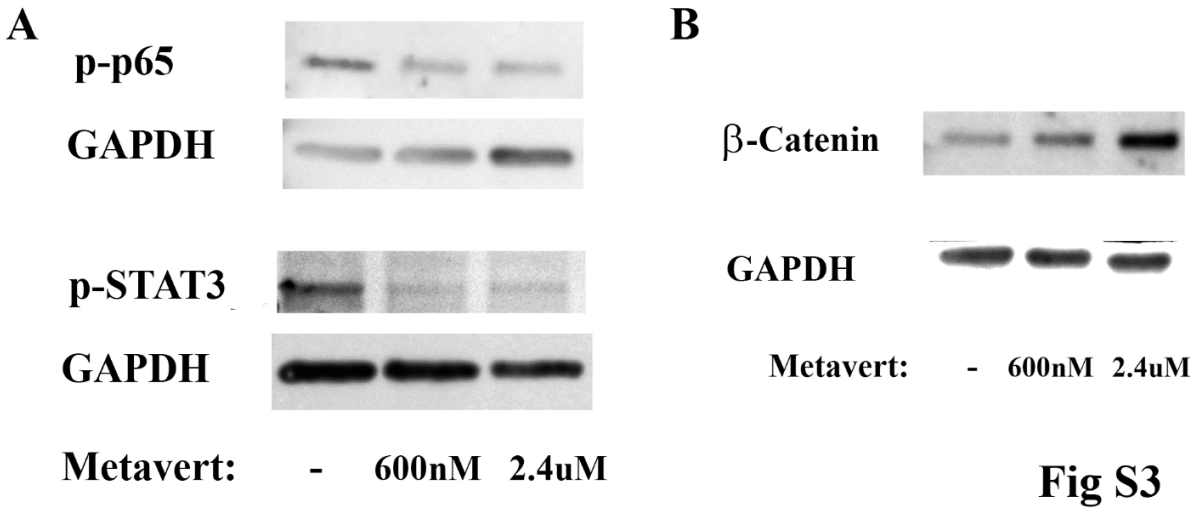

A
p-p65
GAPDH
p-STAT3
GAPDH
Metavert: - 600nM 2.4uM
B
β-Catenin
GAPDH
Metavert: - 600nM 2.4uM

Fig S3

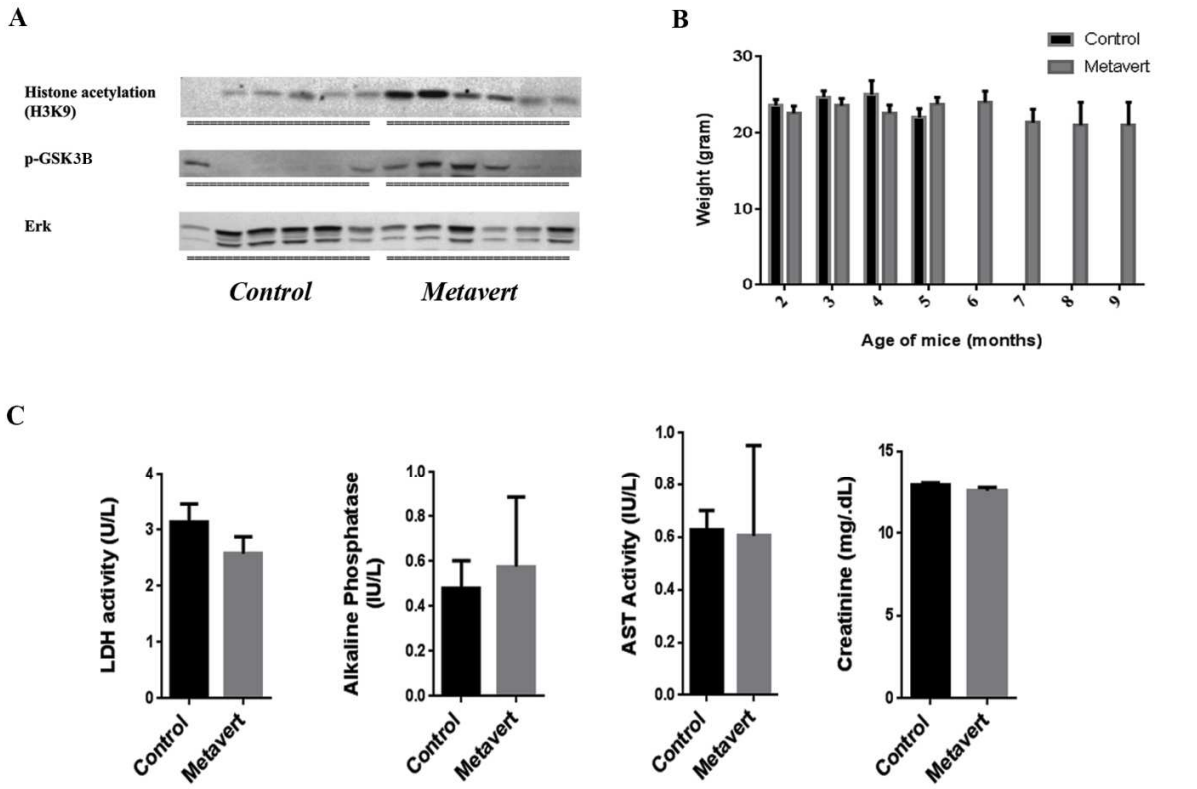
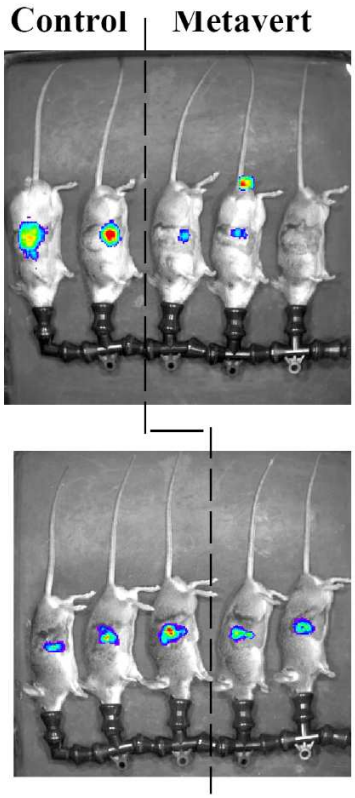

A
Histone acetylation (H3K9)
p-GSK3B
Erk
Control
Metavert
B
Control
Metavert
Weight (gram)
Age of mice (months)
C
LDH activity (U/L)
Alkaline Phosphatase (IU/L)
AST Activity (IU/L)
Creatinine (mg/.dL)
Control
Metavert
D
Control
Metavert
E
Control
Metavert
a
b
c
d
F
Control
Metavert
a
b
c
d

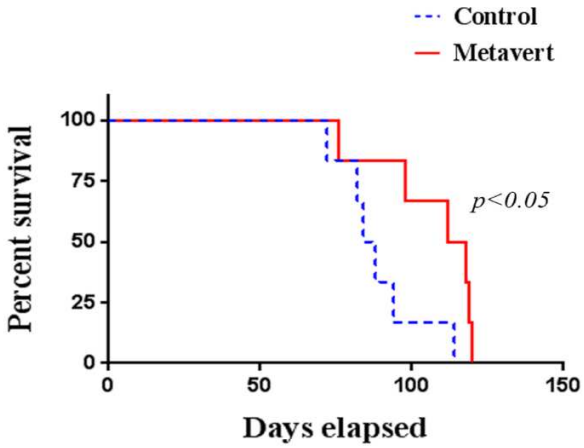
Fig S4

A

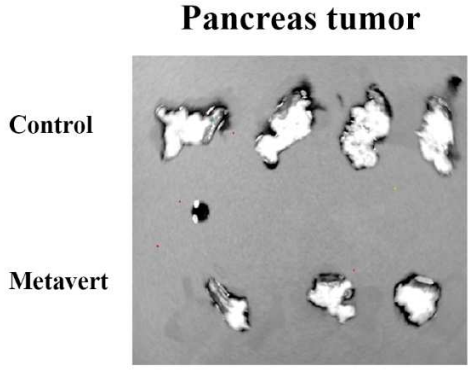


Mean flux: (10^5 p/s) 6.8 (-/+ 1.1) *(p<0.05)* 3.5 (-/+ 0.4)

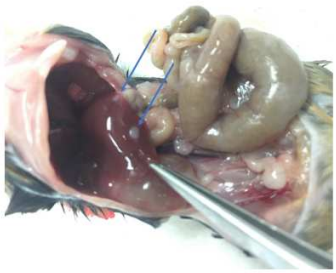
B



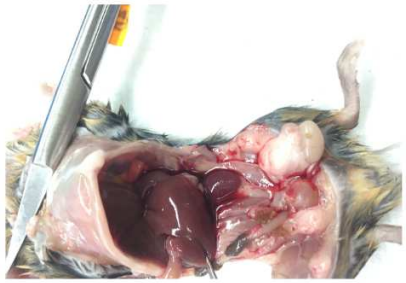
C



D



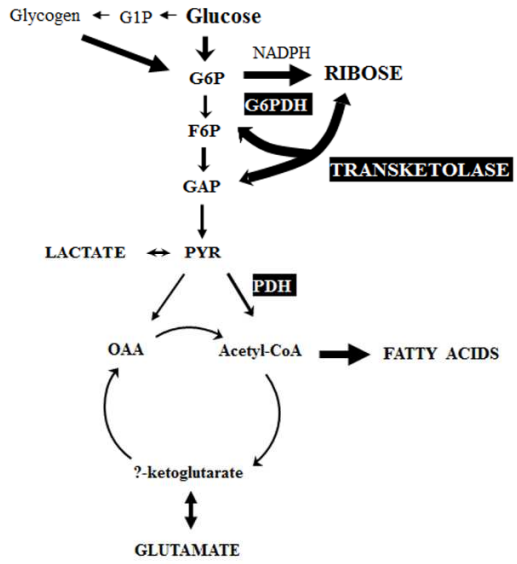
Control



Metavert

Fig S5

Control cancer cell



Cancer cell treated with Metavert

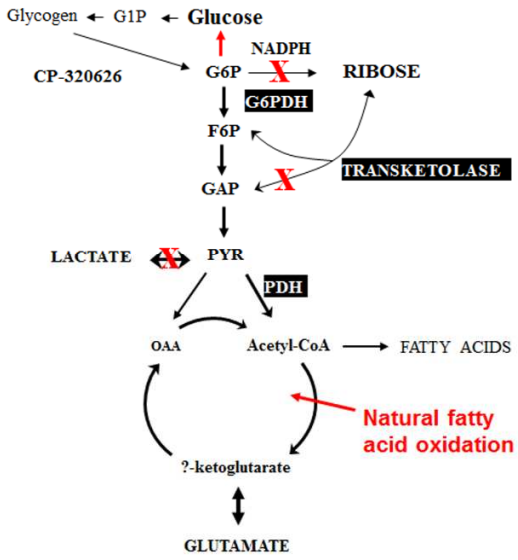


Fig S6