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Proteomic profiling of gemcitabine-resistant pancreatic cancer cells unravels microtubule-associated protein 2 overexpression, that correlated to poorer survival but also to increased sensitivity to nab-paclitaxel

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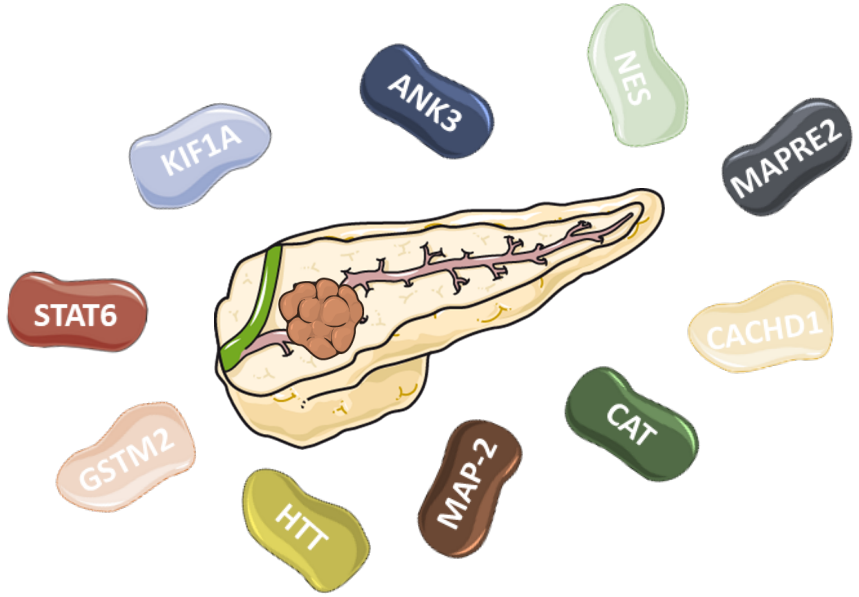
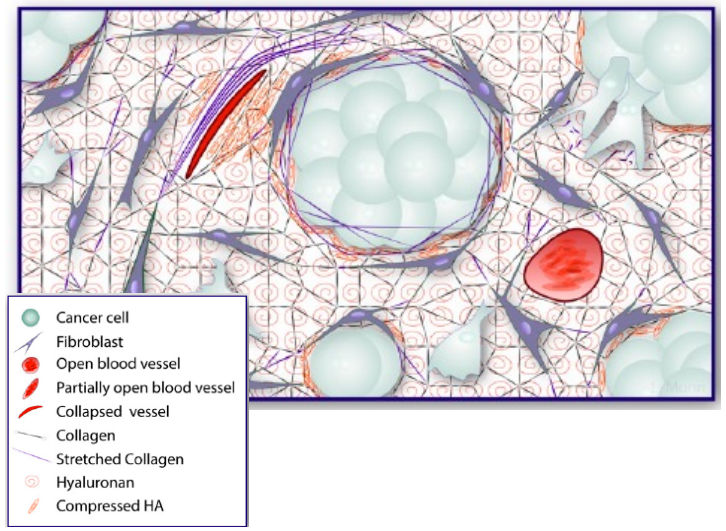


Gemcitabine chemoresistance

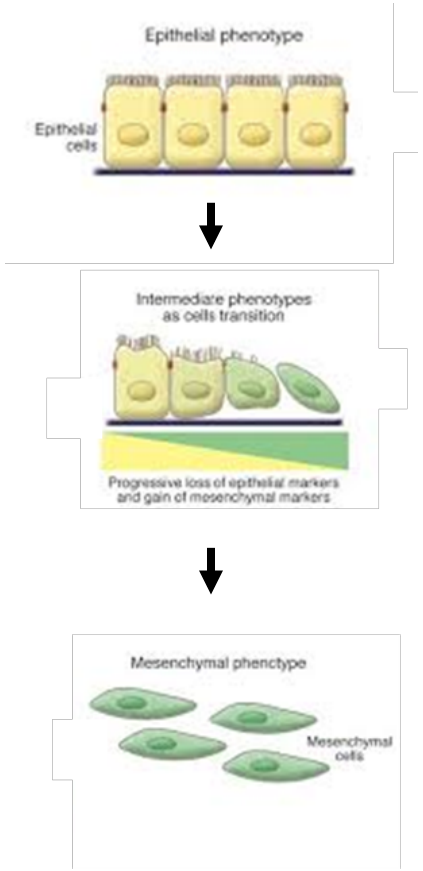
Extrinsic factors

Desmoplastic response

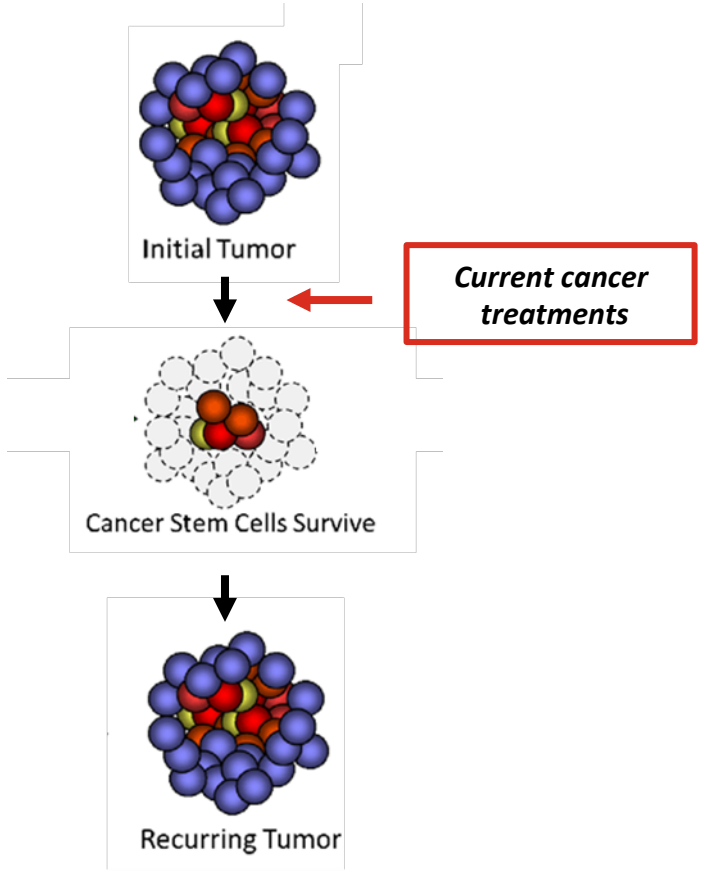


Intrinsic factors

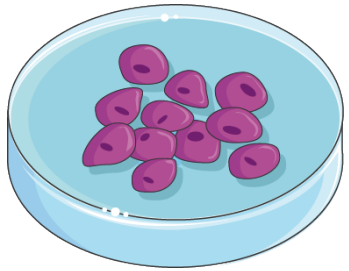
Epithelial-mesenchymal transition



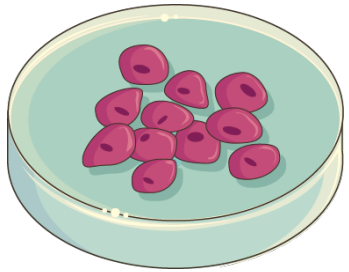
Cancer Stem Cells



In vitro characterization of gemcitabine-resistant PDAC cells



PANC1



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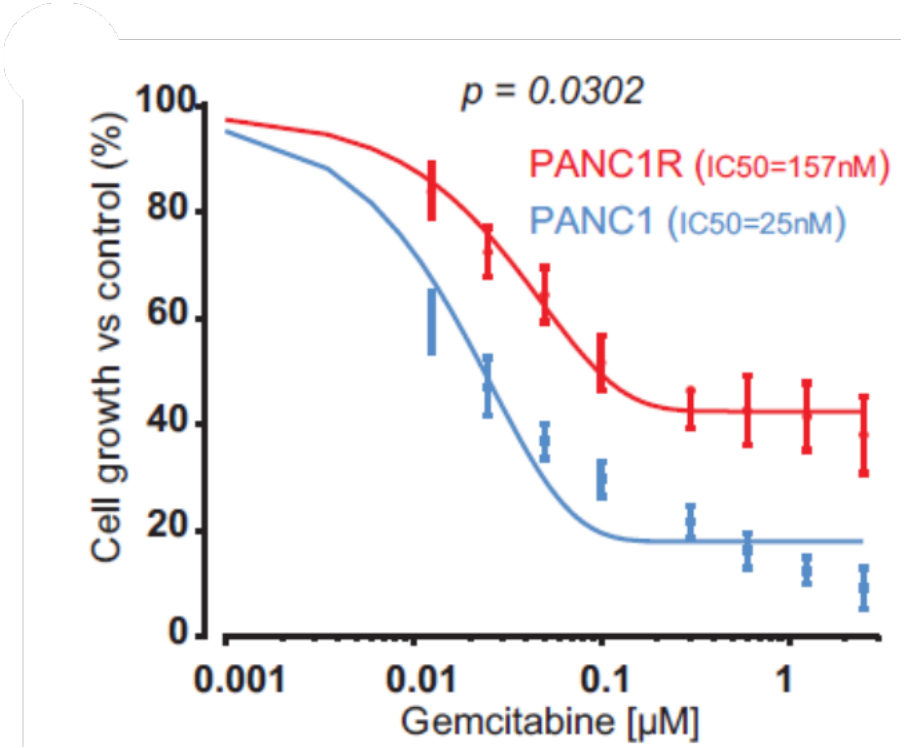
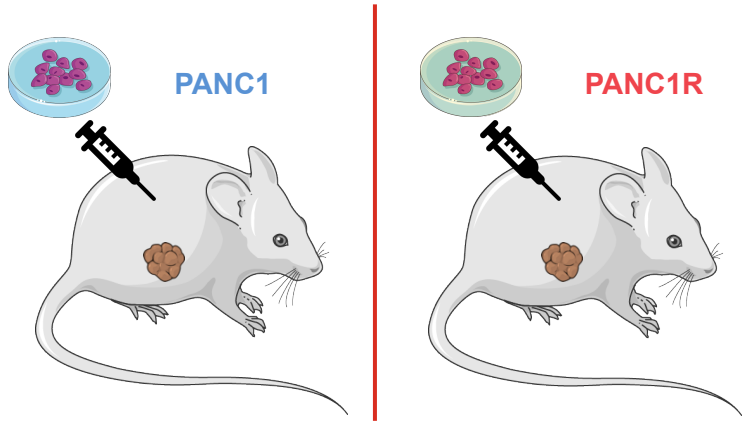
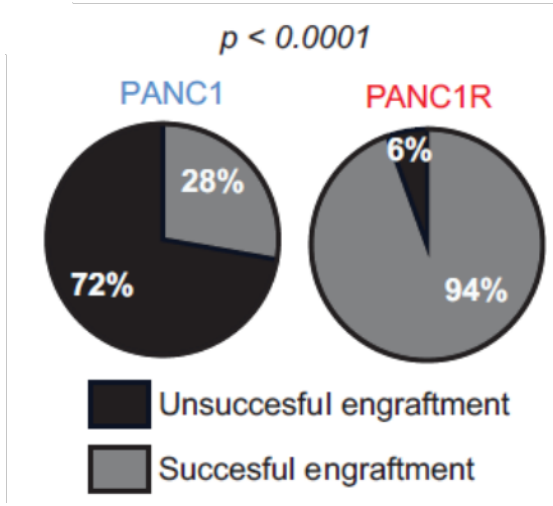
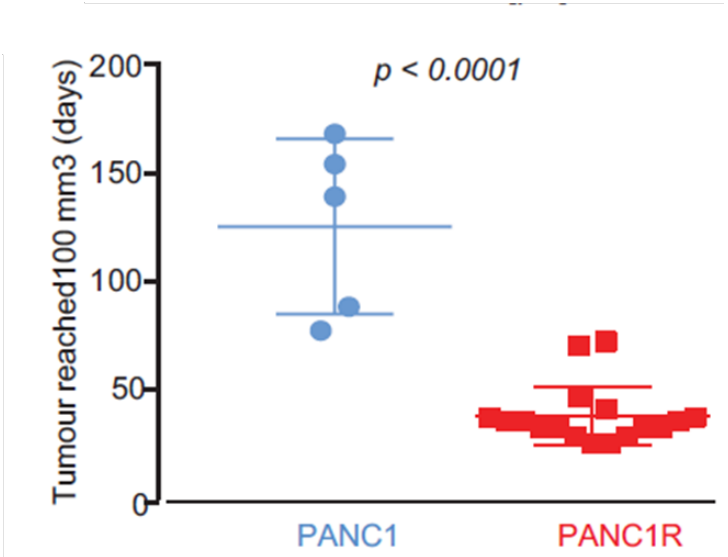
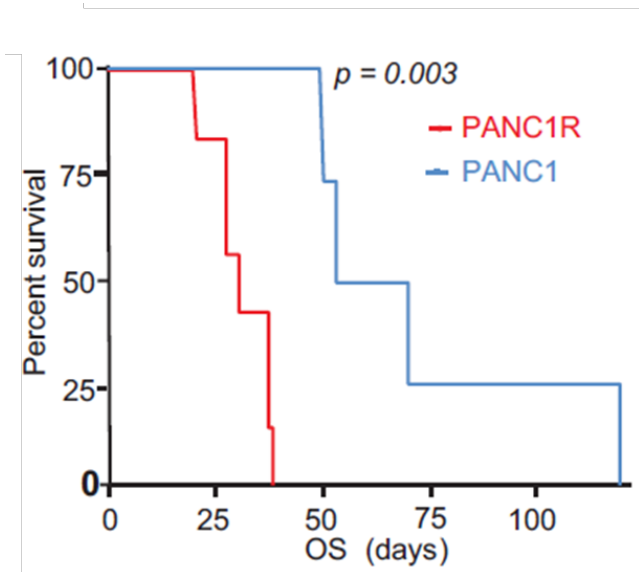


In vivo characterization of gemcitabine-resistant PDAC cells



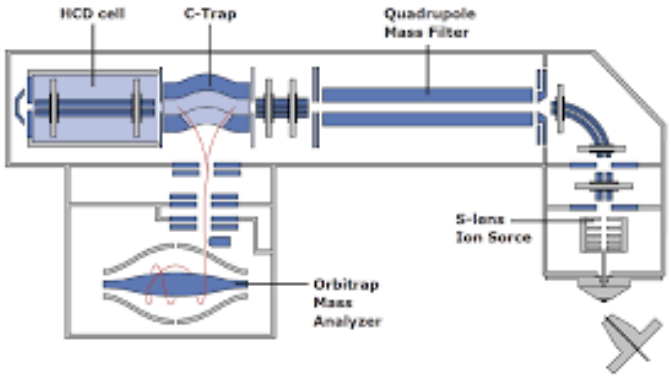






Up-regulated proteins in gemcitabine–resistant PANC-1 cells *versus* sensitive cells

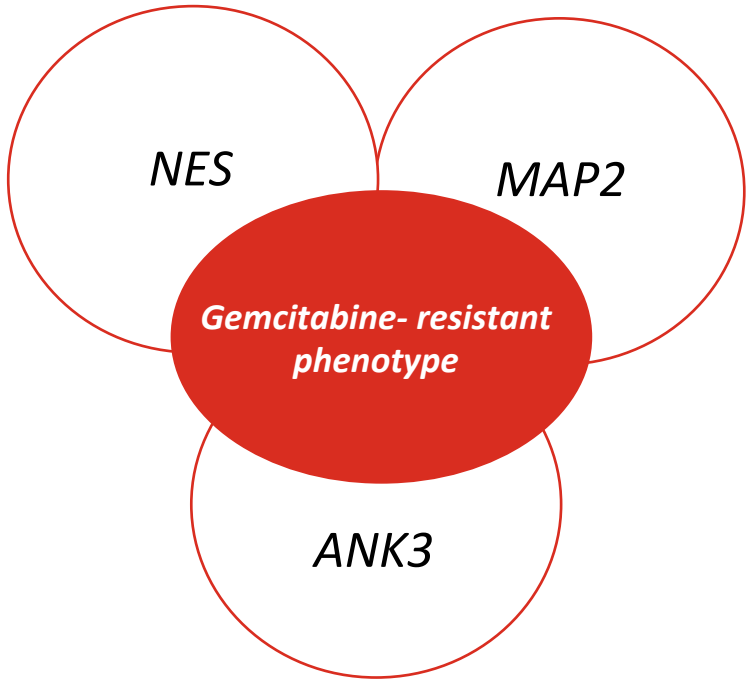
LC-MS/MS



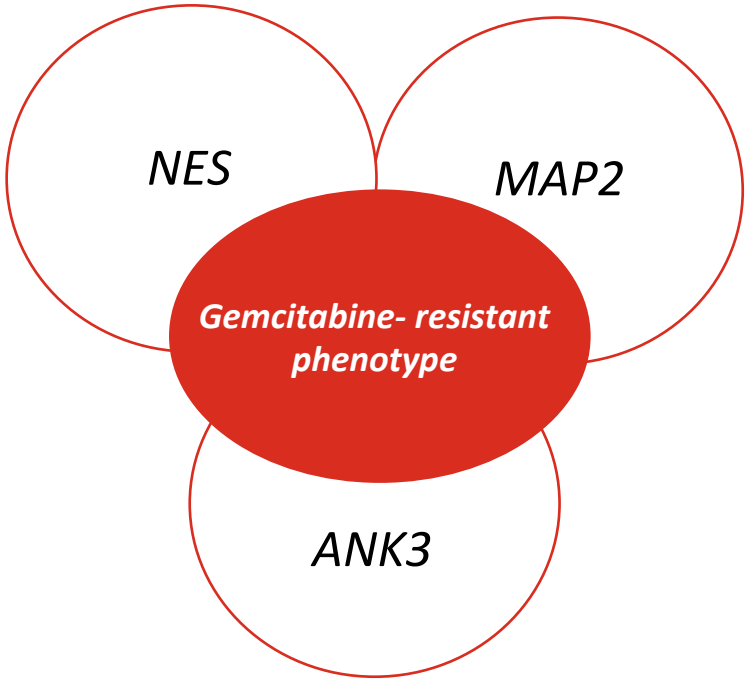
Top 10 upregulated proteins

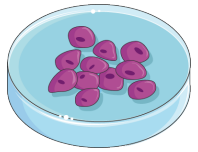
gene name	protein name	*p* value	FC
MAP2	Microtubule-associated protein 2	0.0002	10.18
ANK3	Ankyrin-3	0.0005	22.81
NES	Nestin	0.0006	6.33
CAT	Catalase	0.0013	2.52
KIF1A	Kinesin-like protein KIF1A	0.0018	4.49
STAT6	Signal transducer and activator of transcription 6	0.0019	NA
HTT	Huntingtin	0.0019	2.58
GSTM2	Glutathione S-transferase Mu 2	0.0020	NA
CACHD1	VWFA and cache domain-containing protein 1	0.0028	NA
MAPRE2	Isoform 4 of microtubule-associated protein RP/EB family member 2	0.0028	NA

FC, fold change; PANC1, gemcitabine-sensitive cell line.

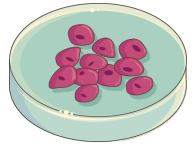


Up-regulated proteins in gemcitabine–resistant PANC-1 cells *versus* sensitive cells

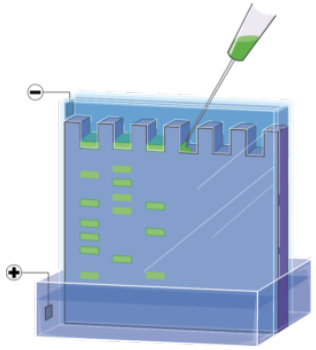


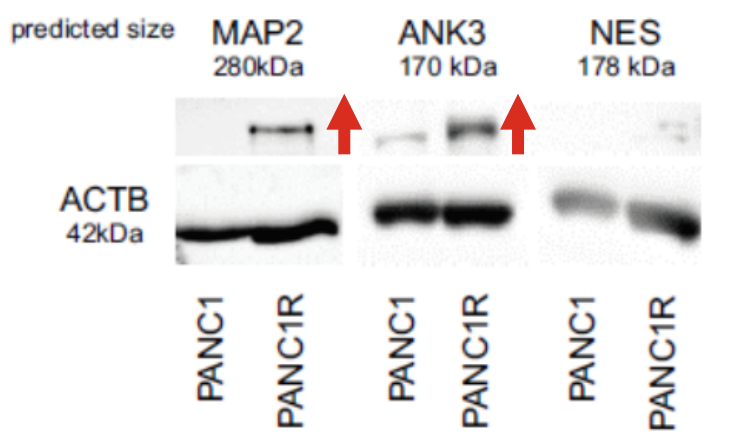


PANC1

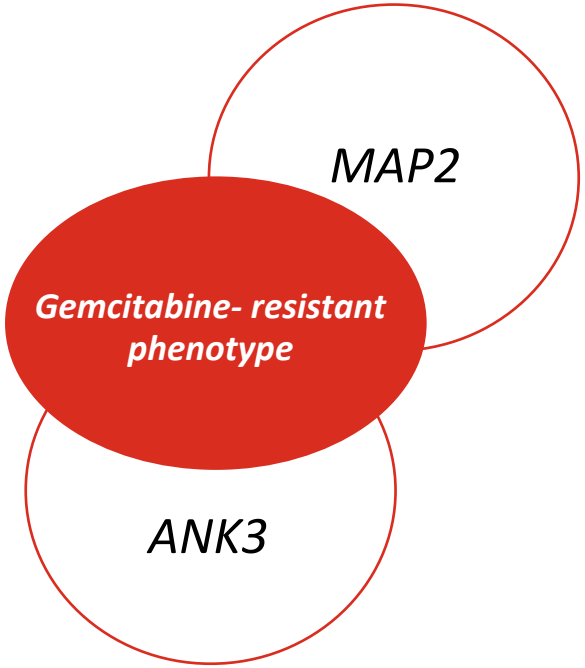


PANC1R





Validation of ANK3 as prognostic biomarker in gemcitabine treated patients

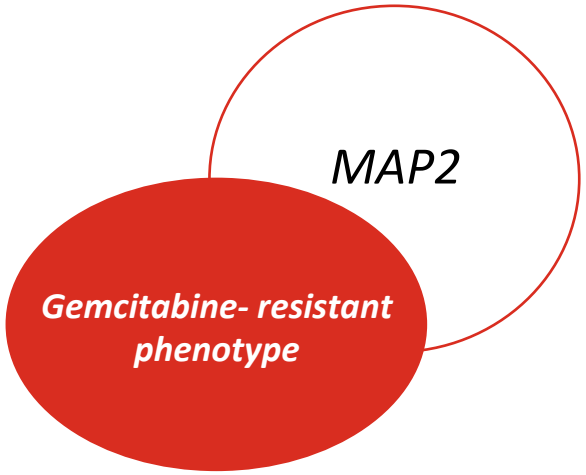


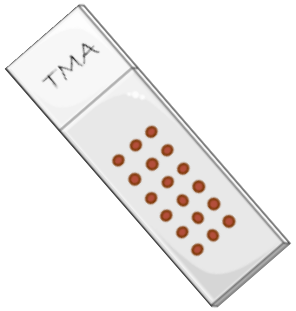
Metastatic cohort ***n* = 36**

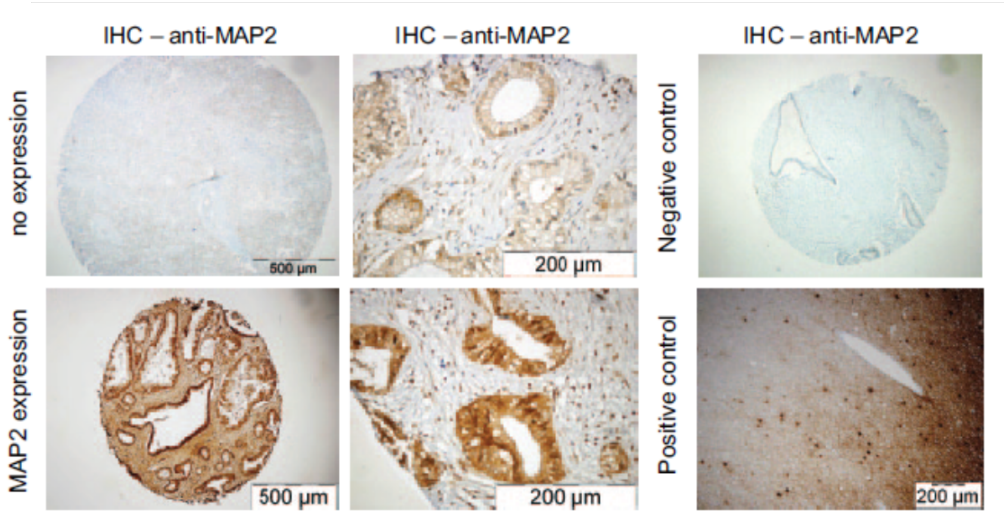
Adjuvant cohort ***n* = 86**

ANK3 was expressed at equal levels in all tumours and scoring on hight versus low expression did not predict gemcitabine resistance

Validation of MAP2 as prognostic biomarker in gemcitabine treated patients

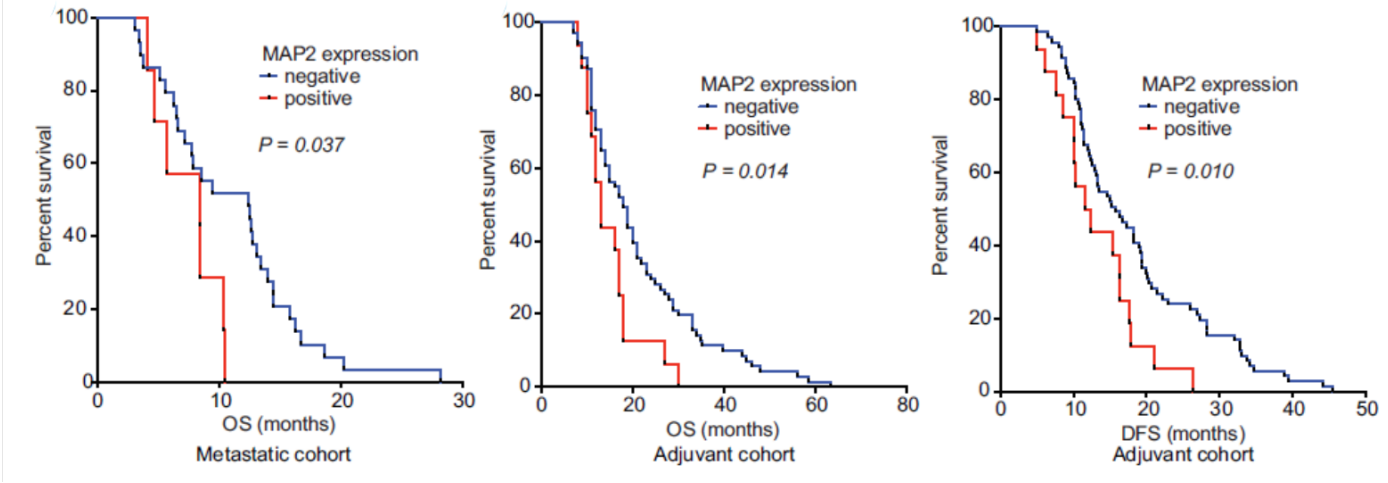




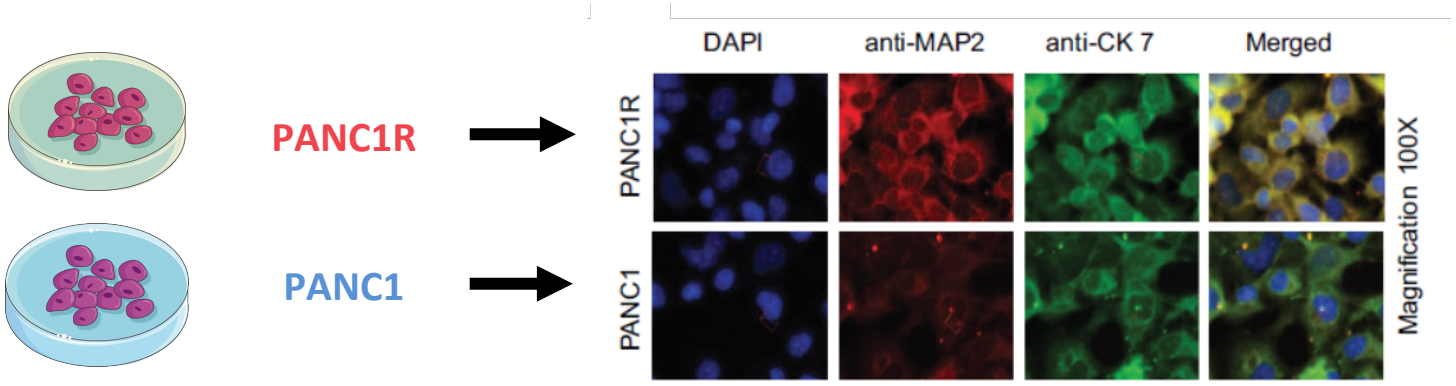


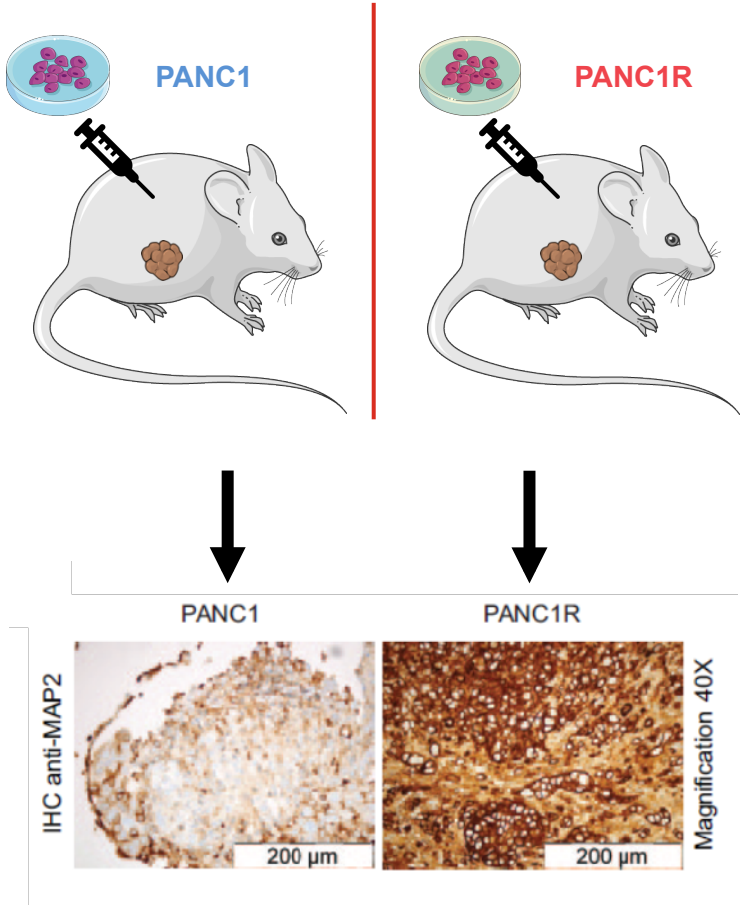
Metastatic cohort ***n* = 36**

Adjuvant cohort ***n* = 86**

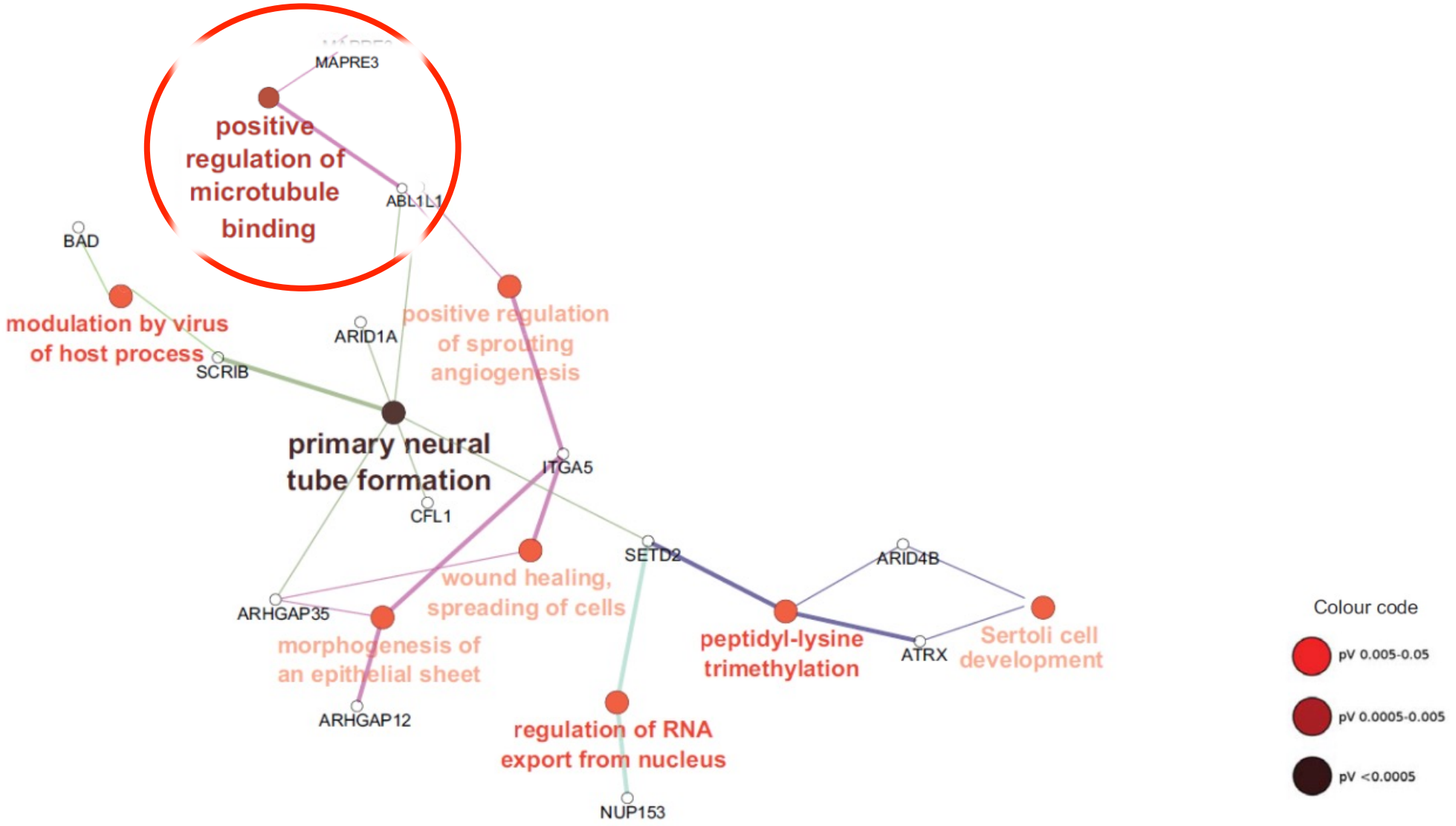


Validation of MAP2 as predictive biomarker of gemcitabine sensitivity

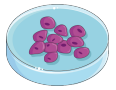




Differential protein expression and pathway analysis

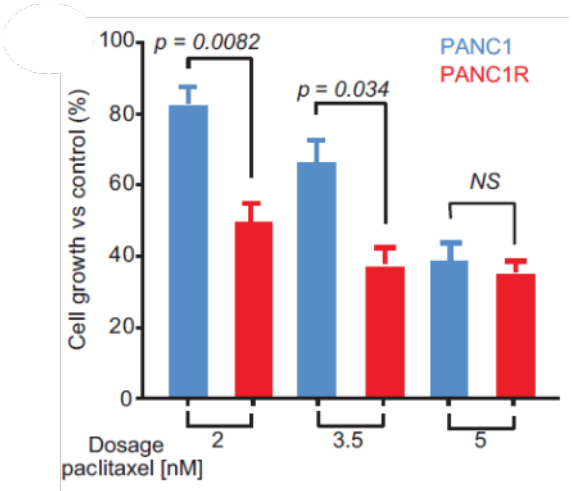


Exploration of microtubule inhibitors as a therapeutic option

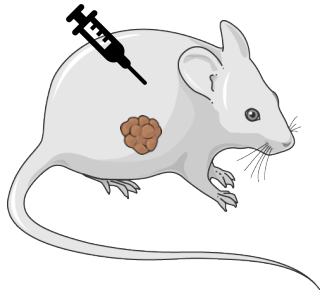


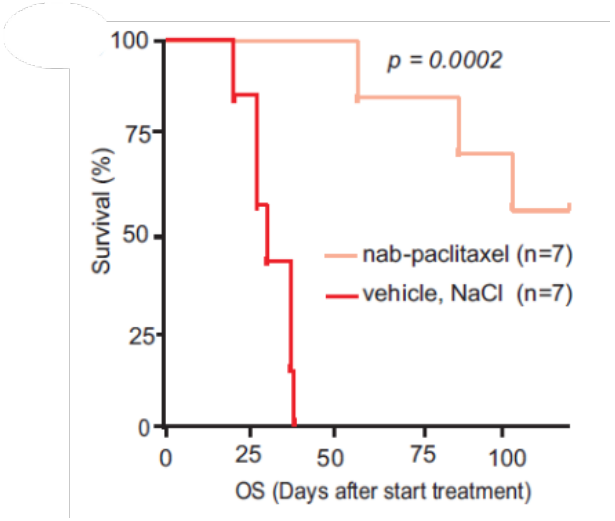
PANC1

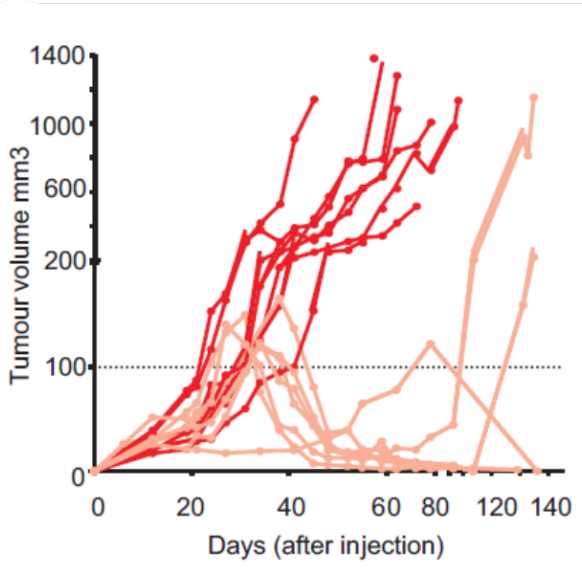
PANC1R

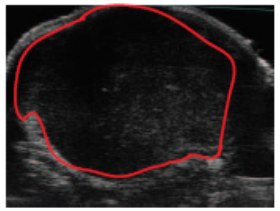


PANC1R



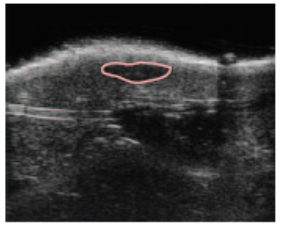






vehicle, NaCl

day 20 (after treatment)

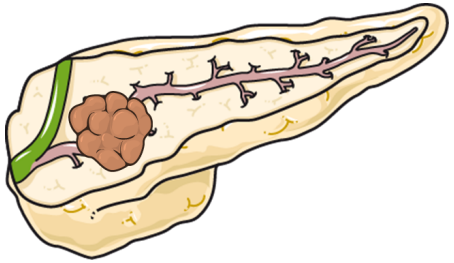


nab-paclitaxel

day 20 (after treatment)

Conclusions

- We unravelled new differentially expressed proteins in a gemcitabine- resistant model of PDAC, including MAP2.



- MAP2- positive staining was validated as a prognostic biomarker in two patients cohorts treated with gemcitabine monotherapy, either in palliative or adiuvant setting. High expression of MAP2 was correlated with poorer survival.

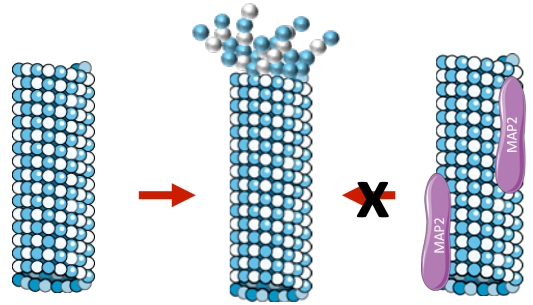
- Phosphorilation of MAP2 is an important regulator of its function, thus guiding microtubule dinamics. Changing microtubules dynamics by higher expression and phosphorilation of MAP2 might result in changed drug transport.

Top 10 upregulated proteins

gene name	protein name	*p* value	FC
MAP2	Microtubule-associated protein 2	0.0002	10.18

Top 10 upregulated phosphopeptides

gene name	protein name	p-peptide sequence	*p* value	FC
MAP2	Microtubule-associated protein 2	VDHGAEIITQSPGRSSVASPR	0.0054	18.04



Conclusions

- We obtained preclinical data, in vitro and in vivo, showing that (nab-)/ paclitaxel was effective against resistant/MAP2- overexpressing cells

- Our findings support the current therapy with gemcitabine and nab-paclitaxel. Part of the success of this combination therapy might be due to cytotoxic effect on resistant cells