ID 0144

Innovative substance 2250, a derivative of taurultam, shows anti-neoplastic effects in malignant pancreatic carcinoma in vitro and in vivo

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In former studies the anti-infective agent Taurolidine (TRD) revealed anti-neoplastic properties against many tumor species *in vitro* and *in vivo*. The anti-proliferative and cell death inducing capacity of TRD is caused by several metabolities a.o. Taurultam (TRLT). In this study it is shown for the first time, that substance 2250 - a newly defined innovative derivative of TRLT – displays an anti-neoplastic effect on malignant pancreatic carcinoma *in vitro* and *in vivo,* along with a longer metabolic stability. In extensive *in vitro* analysis the anti-neoplastic potential as well as the mode of action of substance 2250 was demonstrated, followed by successful and effective *in vivo* testings using xenograft models derived from established pancreatic cancer cell lines as well as patient derived tissue.
This is the first study providing an evaluation of the newly developed substance 2250 induced cell death among several pancreatic cancer cell lines *in vitro* and inhibition of pancreatic tumor growth *in vivo*. In pursuing functional analysis of the involvement of ROS driven and caspase activated programmed cell death we were able to show, that this oxidative stress plays the major role inducing cell death in pancreatic carcinoma. Especially the inhibition of xenograft derived pancreatic cancer tumor growth in mice and the sharply higher metabolic stability of this new substance are strongly relevant towards clinical practice and provide new therapeutical opportunities in pancreatic cancer treatment. These encouraging results build the basis for further functional analysis and first clinical studies for this promising agent.

ID 0168

Rac1b negatively controls transforming growth factor (TGF)-β-induced epithelial-mesenchymal transition and cell motility in pancreatic ductal adenocarcinoma cells by inhibiting both Smad and non-Smad signaling

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Introduction: In pancreatic ductal adenocarcinoma (PDAC), TGF-β1 mediates its prooncogenic effects, e.g. epithelial-mesenchymal transition (EMT) and migration/invasion of tumor cells, in part through the small GTPase Rac1. Prompted by the recent detection of an alternatively spliced Rac1 isoform, Rac1b, in PDAC tissue, we asked whether Rac1b affects EMT and cell motility in the same or in a different way as Rac1.
Methods: Transfection of small interfering RNA (siRNA) was used to selectively knockdown Rac1b. Gene expression analysis was done by real-time PCR, and cell motility was measured by realtime cell migration assay. Results: SiRNA-mediated knockdown of Rac1b in the PDAC cell lines Panc1 and Colo357 attenuated the TGF-β1-dependent down-regulation of E-cadherin but amplified the TGF-β1 response of various other genes involved in EMT (Snail, Slug), and migration/invasion (PAI-1, MMP2, MMP9). Moreover, siRNA-mediated silencing of Rac1b enhanced the ability of TGF-β1 to stimulate cell motility, while cosilencing of Rac1 and Rac1b, or ectopic expression of Rac1b in Panc1 cells attenuated TGF-β1-induced cell migration. The promigratory effect of Rac1b depletion was alleviated by pharmacologic or siRNA-mediated inhibition of Smad3, but not Smad2, by pharmacologic inhibition of p38 mitogen-activated protein kinase, or by ectopic expression of dominant-negative mutants of either p38 or MKK6. The Rac1b-deficient cells exhibited elevated levels of phosphorylated forms of Smad3 and p38.
Conclusions: The results suggest that Rac1b counteracts TGF-β1-induced EMT and, in contrast to Rac1, acts as an antagonist of TGF-β1-dependent cell motility by negatively regulating both canonical (Smad3) and non-canonical (p38) signaling.

ID 0207

Response to 6 cycles of chemotherapy with FOLFIRINOX is predictive of overall survival in patients with locally advanced unresectable pancreatic cancer

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Aim: Retrospective monocentric analysis of outcome of patients with newly diagnosed locally advanced unresectable pancreatic cancer (cM0) after induction chemotherapy with FOLFIRINOX.
Methods: Between 4/2012 and 7/2015 27 patients (13 female, 14 male) underwent induction chemotherapy with 6 cycles FOLFIRINOX(Calciumfolinate 400mg/m²BSA d1, Irinotecan 180mg/m²BSA d1, Oxaliplatin 85mg/m² BSA d1, 5-FU 400mg/m²BSA d1 and 2400mg/m²BSA over 48h).
Median age was 65 years (range: 45–78).
Median Follow-Up was 52 weeks (range: 16–160).
Results: All patients received 6 cycles of FOLFIRINOX. In 14 patients(52%) a dose reduction was performed.
After 6 cycles of FOLFIRINOX 14 patients(52%) showed CT-morphologic partial remission, 9 patients(33%) showed stable and 4 patients(15%) progressive disease.
After 1 year cumulative overall/progression-free survival (OS/PFS) was 70,8%/56,4%.
By comparing responders (partial remission, stable disease) and non-responders (progressive disease) after 6 cycles of FOLFIRINOX the responders showed a cumulative 1year-OS of 87,9% and the non-responders of 0% (log-rank-test: $p < 0.0001$).
None of the non-responders showed a response to a second-line chemotherapy.
In the further course of treatment a tumor resection (8xR0-resection, 1xR1-resection) could be performed in 9 out of 27 patients(33%).
After 1 year patients who underwent tumor resection showed a cumulative OS of 83,3%, patients without resection showed a 1year-OS of 64% (log-rank-test: $p = 0,51$).
Conclusion: In patients with locally advanced unresectable pancreatic cancer response to 6 cycles of chemotherapy with FOLFIRINOX correlates significantly ($p < 0,0001$) with OS. In one third of patients a tumor resection could be achieved.

ID 0233

Correct decision processes are essential in curative therapy of gallbladder cancer

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Background: The S3 guidelines valid till 2015 have recommended radical re- resection (RR) in up to T2 stages. The new guidelines recommend RR even in T1b. According to the data of the German- registry the indication for RR in Germany depends more on the experience of the hospitals in liver surgery than on complying with the guidelines, so most of IGBC`s are staged and not treated oncological sufficiently. In practice there are the following questions asked. Is the biologic behavior of GC underestimated? Depends the therapy of patients with IGBC in Germany on the surgical or oncological expertise of the clinics? Which technique of liver resection (LR) is meaningful in which stage? What is important regarding lymph node ratio (LNR).
Methods: For data analysis, we used the German Registry.

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