Results and discussions Treatment of different PDX-derived cell lines with the combination of taxanes and CDK4/6 inhibitors resulted in a higher anti-proliferative effect than both drugs used as single agent. Cell cycle studies showed that inhibition of CDK4/6 prevented recovery from treatment with taxol. At the molecular level we found that the combined treatment induced a clear interruption in retinoblastoma pathway, even higher than CDK4/6 inhibition in monotherapy. Gene expression profiles comparing single versus combined treatment are currently being performed to further understand the molecular basis underlying the effectiveness of this type of treatment. Moreover, to assess the efficacy of this new combined treatment in vivo, we treated nine PDAC PDX models with PD-0332991 and nab-paclitaxel, following the same schedule. Importantly, eight of them presented an increased tumour growth inhibition in the combination with respect to the monotherapies.

Conclusion Although the molecular mechanism underlying the effectiveness of this treatment is not completely understood yet, our data suggest a good therapeutic value for the combination of CDK4/6 inhibitors and taxanes in PDAC treatment.

PO-029 ANGIOTENSIN-(1–7) PROMOTES MIGRATION OF RENAL CELL CARCINOMACELLS WITH NO EFFECT ON CELL PROLIFERATION

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Introduction Renal Cell Carcinoma (RCC) is the most common kidney with still unclear pathophysiology. The most common types of RCC are clear cell (ccRCC) and papillary (pRCC). Recently, it has been proposed that renin-angiotensin system (RAS), mainly including angiotensin II, is involved in development and progression of RCC. Angiotensin-(1–7) (Ang-(1–7)) is a RAS molecule, acting through Mas receptor (MasR), that has recently gained more attention because its ability to inhibit proliferation and migration of lung, breast and prostate cancer cells. Because high levels of Ang-(1–7) are observed in the kidney, we have decided to investigate role of Ang-(1–7) on RCC cells.

Material and methods The study was performed on Caki-1 and Caki-2 cell lines that represent ccRCC and pRCC phenotype respectively. Cell proliferation was assessed by AlamarBlue assay and wound healing assay was used for quantification of cell migration. Cell were treated with different combinations of 0.001–10 uM of Ang-(1–7) and/or MasR antagonist A-779 for 6–72 hour depending on the experiment.

Results and discussions We found that Ang-(1–7) increase cell migratory abilities of both Caki 1 and Caki 2 cells after 6, 12, 18 and 24 hour (p<0.01). The effect is inhibited by blockade of Mas receptor by A-779, that have no effect on migration when administrated alone. In the proliferation assay, 0.1 uM Ang-(1–7) caused 20% increase of cell proliferation, while 1 uM A-779 inhibited proliferation up to 30%, however, both results were not statistically significant (p>0.05)

Conclusion This study demonstrates potential role of Ang-(1–7) and Mas receptor in pathogenesis of RCC, mostly by promoting cell migration and increasing metastatic potential. Results may help to better understand molecular mechanism underlying progression of this tumour and find new potential targets for therapy. Discrepancy between pro-migratory effect and no impact on cell proliferation, role of Ang-(1–7) and MasR requires further studies and confirmation in animal model of RCC.

PO-030 FUNCTIONAL ANALYSIS OF MASTL MUTATIONS IN CANCER

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Introduction Mastl, also known as Greatwall, is a protein kinase essential for proper chromosome condensation and progression through mitosis and meiosis. It belongs to the AGC kinase family and, particularly, presents a non-conserved insertion of 550 aa at the corresponding T-activation loop site in the C-lobe (usually 20–30 aa). This non-conserved middle region (NCMR) is not considered to have an essential role for Mastl activity but its function in unknown. Mastl is involved in the inhibition of protein phosphatase 2A (PP2A)-B55 complexes to maintain the mitotic state. By using a conditional knockout in mouse generated in our lab, it was shown that mammalian Mastl is essential for mouse embryonic development and cell cycle progression. Mastl was initially found in humans as a gene mutated in thrombocytopenia and preliminary data suggests its overexpression in tumours. However, very little is known about this protein in human disease.

Material and methods Genomic data from repositories of cancer somatic mutations include MASTL NCMR indel mutations, leading to the generation of a truncated protein. Exome sequencing studies in Mastl in gastric cancers show that mutant tumours present microsatellite instability (MSI). We have studied the prevalence of these mutations by sequencing MASTL in a subset of samples from colon and stomach patients.

To evaluate the therapeutic relevance of this kinase, functional assays have been performed, as complementation studies and kinase assays.

To mimic the cancer mutations we have generated a new mouse model using CRISPR/Cas9 technology. We are currently performing several assays such as focus assays, scratch assays, soft agar and colony formation on cells derived from this model. In addition, we are using a chemical-induced colorectal carcinoma model to study the role of these mutant kinases in cancer.

Results and discussions A heterozygous exonic indel mutation has been found in an MSI +CRC from the 21 patient samples sequenced.

Functional assays with the mutant enzyme resulted in a partial rescue in DNA segregation observed in Mastl-null cells.

Mastl mutant forms resulted in embryonic lethality in homozygosis. Therefore, our carcinogenesis models are performed in heterozygous mice, thus mimicking cancer mutations.

Conclusion Mastl indel mutations in the NCMR region lead to the expression of truncated shorter forms. These Mastl mutated forms are not able to fully accomplish the role of Mastl in mitosis. Mutant heterozygous mice, mimicking MASTL cancer mutations, are viable and fertile.