tumour-stroma integrations, promoting tumour development and metastatic spread. Few effective therapies mean that PDAC is predicted to be the second leading cause of cancer mortality by 2030. In highly metastatic mouse models of PDAC, we observed enhanced extracellular matrix (ECM) deposition and remodelling throughout disease progression. This was paralleled by an increased focal adhesion kinase (FAK) expression and activity, suggesting a role for FAK in the increased desmoplastic reaction that is typical of PDAC. Consequently, fine-tuned manipulation of the dense stroma by streamlined FAK inhibition (FAKi) presents a novel opportunity for PDAC management and improved response to chemotherapy.

**Material and methods** Intravital imaging of the FUCCI cell cycle reporter was used to dynamically monitor tumour cell response to combined FAKi and standard-of-care therapy with gemcitabine/Abraxane. This was overlaid with second harmonic generation (SHG) imaging of collagen fibres, to assess the efficacy of FAKi to disrupt the dense PDAC ECM. To complement our *in vitro* metastatic studies, we used sophisticated 3D *in vivo* models of invasion, anchorage-independent growth and shear-stress, in both primary and patient-derived PDAC cell lines.

**Results and discussions** We systematically demonstrated that using FAKi to modulate ECM prior to standard-of-care therapy enhanced treatment efficacy whilst also reducing metastatic spread *in vivo*. Further analysis revealed that FAKi sensitised cells to shear stress, impairing metastatic colonisation and the establishment of fibrotic niches in the liver. Stratified patient samples revealed a subset of patients likely to respond to FAK priming regimes, where fine-tuned ECM manipulation prior to chemotherapy may offer a novel opportunity in metastatic PDAC.

**Conclusion** This subtype-specific fine-tuned stromal manipulation may allow us to maximise gemcitabine/Abraxane therapy whilst reducing drug toxicity and potentially reducing metastatic spread in a preclinical setting.

**PO-230**

**CYSTEINE-RICH SECRETORY PROTEIN 3 REGULATES PROGRESSION FROM IN SITU TO INVASIVE PROSTATE CANCER**

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10.1136/esmoopen-2018-EACR25.747

**Introduction** One of the most challenging aspects of prostate cancer diagnosis is predicting whether cancer will remain indolent or progress to invasive, aggressive and potentially lethal disease. Current markers such as PSA are unreliable and tumours requiring treatment may remain undetected while others are over-treated. Cysteine-rich secretory protein 3 (CRISP3) is a member of a poorly defined family of proteins that is highly up-regulated in human prostate cancer.

**Material and methods** We sought to define the role of CRISP3 in the molecular pathology of prostate cancer through the generation of a Crisp3 knockout mouse line, which was crossed onto the Hi-MYC mouse model of prostatic adenocarcinoma. The pro-invasive actions of CRISP3 were also studied using human and mouse derived cell lines and purified recombinant CRISP3.

**Results and discussions** Here we show that CRISP3 induces migration and invasion of prostate cancer cells *in vitro*. Furthermore, and consistent with human expression data, CRISP3 was dramatically up-regulated with advanced disease in the Hi-MYC mouse model of prostatic adenocarcinoma and specifically associated with transformed and migratory cells both *in vivo* and *in vitro*. Importantly, Crisp3 deletion delayed the transition from prostatic intraepithelial neoplasia to carcinoma *in situ* and blocked the transition to the invasive disease. These effects are attributed to changes in the expression of EMT markers in response to CRISP3. We are currently validating potential CRISP3 binding partners identified by mass spectrometry.

**Conclusion** Collectively, these data define CRISP3 as prometastatic in the prostate through a role in promoting cancer invasion.

**PO-231**

**CTXIII EXPRESSION AROUND SINGLE TUMOUR CELLS OF INVASIVE BREAST CARCINOMA**

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10.1136/esmoopen-2018-EACR25.748

**Introduction** Studies of breast carcinoma indicated the presence of type I and III collagens localization at the invasion front of the tumour. Mesenchymal invasion accompanied by proteolysis, in particular, collagens, and remodelling of tissue structures by matrix metalloproteases. Possible marker of this process is expression of Cross Linked C-telopeptide of Type III Collagen (CTX-III). The project is aimed to study frequency of CTX-III expression around different of single tumour cells subtypes of invasive breast carcinoma of no specific type.

**Material and methods** Fourteen patients with invasive breast carcinoma of no specific type (IC NST, all molecular subtypes, T1-3N0-3M0) were enrolled in study. CTX-III expression around different subtypes of single tumour cells were analysed in FFPE tumour samples using confocal microscope LSM780 (Carl Zeiss, Germany).

**Results and discussions** CTX-III expression around single tumour cells was observed at 21% of breast cancer patients. In positive cases only 5% of single tumour cells were express CTX-III and these cells have features of stemness, EMT or both.

**Conclusion** Only small part of single tumour cells showed signs of a mesenchymal type of invasion, and it didn’t depend on the state of stem and EMT.

The study was supported by RSF (#16-15-10221).

**PO-232**

**ACTIN-DEPENDENT EFFECT OF TUMOUR SUPPRESSOR P53 ON HUMAN LUNG CANCER CELL MALIGNANT CHARACTERISTICS**

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10.1136/esmoopen-2018-EACR25.749

**Abstracts**
Introduction The enhancement of tumour cell malignant characteristics could be caused by a shift in the ratio of cytoplasmic actin isoforms (β- and γ-) via γ-actin increasing. We have previously shown that γ-actin predominance in neoplastic cells led to tumour progression due to ERK1/2 activation, and vice versa Ras-dependent ERK1/2 activation led to γ-actin increasing. There is probably a positive feedback loop between MAPKs activation and γ-actin level enhancing malignant traits of neoplastic cells. Since MAPKs activation was observed in many human tumours as a result of oncogenes activation and/or tumour suppressors inactivation, it has been important to identify mechanisms that lead to a shift in the ratio of β-/γ-actin. We aimed to study neoplastic cell properties caused by tumour suppressor p53 dysfunction: changes in cytoskeleton, motility, growth rates in vitro and in vivo, metastasis, as well as to identify the molecular mechanisms underlying these changes.

Material and methods We created A549 derivatives expressing exogenous mutant p53 proteins with amino-acid substitutions at positions 175, 248, 273 representing hot-spot mutations, and the subline with TP53 repression induced by shRNAs as well as H1299 cells with both deleted TP53 alleles with exogenous-restored wild type p53 expression.

Results and discussions Inactivation of normal p53 function by exogenous mutant forms with known dominant-negative effect, as well as the TP53 repression in A549 cells led to increased migration and invasion, proliferation, the growth rate of subcutaneous xenografts as well as increased metastasis of intrapulmonary A549 xenografts in nude mice. Exogenous TP53 WT expression in p53-negative cells H1299, on the contrary, suppressed proliferation and migration, significantly reduced orthotopic tumorigenicity and metastasis. The change in cell motility was associated with actin cytoskeleton reorganisation and shift in the actin isoforms ratio. Apparently, the shift in the ratio towards γ-actin predominance occurred as a result of ERK1/2 activation in cells with p53 dysfunction and led to enhanced neoplastic cell malignant properties.

Conclusion Actin cytoskeleton reorganisation via increasing γ-actin level stimulated tumour progression and metastasis as a result of tumour suppressor p53 dysfunction and activation of MAPKs so γ-actin predominance could be a universal characteristic of neoplastic cells. The study was supported Russian Science Foundation (RSCF), grant No. 14-15-00467.

Here we examined the effect of interference with DOCK1 function on Ras-driven cancer cell survival and invasion.

**Material and methods** Endogenous expression of DOCK1 in various mouse and human cancer cells harbouring oncogenic Ras mutations was ablated by gene targeting, shRNA expression, and CRISPR-mediated genome editing. Invasive activity was measured by using the Matrigel invasion chambers. Macropinocytic activity was assessed by measuring the cellular uptake of fluorescent dextran. Cell survival was assessed under glutamine-deprived conditions. For in vivo metastasis, cells were injected into the tail vein of C57BL/6 mice. In vivo tumour growth was assessed by inoculating cancer cells into the back of BALB/c nude mice. TBOPP, a selective inhibitor of DOCK1 that binds to the catalytic domain of DOCK1 and blocks its GEF activity, was administered into mice intravenously or by using microinfusion pump.

**Results and discussions** Interfering with DOCK1 function by genetic inactivation and pharmacological inhibition markedly suppressed invasion, macropinocytosis, and survival under low nutrient conditions in various cancer cells. Furthermore, TBOPP treatment suppressed cancer metastasis and growth in vivo in mice.

**Conclusion** Our results demonstrate that DOCK1 plays a critical role in malignant phenotypes of Ras-driven cancer cells. Thus, selective inhibition of DOCK could be an effective approach to target cancer cell survival and invasion.

**PO-234 ABSTRACT WITHDRAWN**

**PO-235 INTEGRIN BETA-LIKE 1 OVEREXPRESSION STIMULATES INVASIVENESS OF OVARIAN CANCER CELLS IN VITRO**

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10.1136/esmoopen-2018-EACR25.751

**Introduction** In our previous microarray study we analysed gene expression profile of over 100 ovarian cancer samples. We identified two molecular subgroups of high grade serous ovarian cancers (HG-SOC) with distinct gene expression profiles and survival. Among differentially expressed genes was an Integrin beta-like1 gene (ITGBL1). ITGBL1 is a poorly characterised protein, structurally cognate with integrin β. Our aim was to study whether and how ITGBL1 can influence the phenotype of ovarian cancer cells.

**Material and methods** ITGBL1 coding sequence was PCR-amplified from cDNA and cloned into pLNCX2 vector. Retroviral system was used to obtain two ovarian cancer cell lines: OAW42/ITGBL1(+) and SKOV3/ITGBL1(+) with overexpression of ITGBL1. Control cell lines were obtained by transduction with empty vector. A Matrigel cell invasion assay was performed using 24-well transwell inserts (coated with fibronectin and matrigel). Crystal violet staining of invaded cells was performed, then the dye was solubilized with 10% acetic acid and the absorbance was measured at a wavelength of 595 nm.