controls. A total of 215 tumor samples excised from patients have been transplanted for patient-tumor derived model development; and a total of 78 xenograft tumor models have been established with a tumor taking rate of 36%. The tumor taking rates of different tumor types were non-small cell lung cancer (40%), small cell lung (50), colorectal (46%), gastric (37%), ovarian (40%), renal cell carcinoma (15%), and acute lymphocytic leukemia (20%). The tumor taking rates were higher in the later passages than earlier passages for the various tumor types, ranged from approximately 50–100%. The positive control drugs tested against the patient-tumor derived models included paclitaxel, docetaxel, irinotecan, doxorubicin, 5-FU, gemcitabine, and tarceva; they produced tumor inhibition rates ranged from 30−70%, which were consistent with their clinical findings. The patient-tumor xenograft tissues from all 5 generations presented a similar histopathological morphology and genomic profile to human primary tumors. These results suggest that patient-tumor derived xenografts provide a unique renewable source of tumor material for test of novel anticancer agents and may predict more relevant clinical response rate and higher correlation with clinical findings than use of xenograft models established from long-term cultured cancer cell lines. Especially, they have advantages for test of target-oriented therapeutics in new drugs development programs.

263 POSTER

A non-invasive bioluminescent imaging technique for monitoring shutdown of the tumour vasculature

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In the preclinical development of vascular disrupting agents (VDA) a key pharmacodynamic endpoint is demonstration of shutdown of the functional tumour vasculature. This is usually done by injecting a dye which labels the functioning blood vessels, e.g. Hoechst 33342, immediately prior to sacrifice and evaluating vascular profile density in tumour cryosections. This is not ideal as it only gives indication of shutdown at a fixed time-point, and shutdown is not assessed over time in the same animal. With non-invasive bioluminescent imaging (BLI) techniques detection of tumour deposits is reliant upon the conversion of an injected substrate, luciferin by luciferase present in the tumour cells resulting in light emission. We hypothesise that by closing down the tumour vasculature with a VDA the amount of luciferin that can reach the tumour cells will be restricted, and thus reduce the emitted light.

In this study we used non-invasive BLI to assess the effect of a novel colchicine-derivative VDA, ICT-2552 on a subcutaneously implanted DLD-1 human colorectal adenocarcinoma cell line engineered to express luciferase.

Optimal shutdown time was initially determined using BLI and compared to the Hoechst 33342 method at 1, 4 and 24 hours post-treatment, using different mice for each time point. Both methods indicated vascular shutdown at 1 and 4 hours, with re-establishment by 24 hours. In a further experiment, Cisplatin which should not affect the vasculature was included as a control agent, with evaluation at 1 and 24 hours post-treatment. As seen previously, both methods indicated reductions in tumour vasculature in the ICT-2552 group at 1 hour ($p < 0.05$), with recovery by 24 hours. No significant change was seen for Cisplatin.

Having demonstrated that BLI can be reliably used to measure vascular shutdown, a further BLI study was carried out monitoring shutdown in the same animal over time at 1, 6 and 24 hours following treatment with either ICT-2552 or 2 more standard agents which should not affect the tumour vasculature, 5-Fluorouracil and Doxorubicin. Vascular shutdown was seen at 1 and 6 hours in those mice treated with ICT-2552 ($p < 0.05$) whilst signals remained stable or increased in those mice treated with the control drugs.

In conclusion, we have demonstrated that BLI is a realistic alternative to invasive methods in evaluating vascular shutdown, with the advantage of being able to follow the same animal throughout a study thus reducing animal use.

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Establishment of a targeted fluorescence guided colonoscopy for a xenograph orthotopic colorectal cancer model

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Introduction: Many GI tract tumors are derived from early metaplastic and dysplastic changes of the mucosa that so far are missed by conventional endoscopic imaging approaches in 25−30% of patients. Potential applications for near-infrared contrast agents are detection of gastrointestinal tumors by fluorescence-guided endoscopy. Despite many published orthotopic tumor models of CRC none of them is appropriate for monitoring xenograph tumor growth by an fluorescent-guided endoscopy.

Material and Methods: Our xenograph orthotopic tumor model is implanted in the Colon descendens of nude mice. Tumor growth and spread out of metastasis were monitored by Bioluminescence Imaging. Endoscopy started on day 1 after surgery and was repeated once a week. For monitoring size and grading of the tumors in the lumen a score sheet was prepared and validated. In addition fluorescence-guided endoscopy was established by combining the rigid endoscope (STORZ) with a fiber probe (Manu Kea). For the fluorescence endoscopy the animals received a targeted fluorescene imaging agent (IntegrisSense 680, VISEN) 24 hours before imaging. This potent, selective non peptide molecule is an $\alpha_v\beta_3$ antagonist and a Near- Infrared- fluorochrome. With this technique we are able to visualize and to quantify the integrin $\alpha_v\beta_3$ expression in colorectal tumors.

Representative mice were also imaged in a μCT. At the end of each study the colons including the tumors were taken out for further immunohistochemical analysis including HE, Cytokeratin, CD31 and Ki67 staining.

Results: Tumor growth of different cell lines could be monitored by endoscopy and bioluminescence imaging. We could combine the fiber endoscope with the rigid endoscope and we could clearly distinguish healthy mucosa from early stages of tumor tissue. The small tumors could also be detected by negative contrast in the μCT post rectal injection of BaSO4 (positive contrast agent). Accordingly, immunohistochemical analysis of the tissues revealed human cells growing in the colon, which were positive for PanCytokeratin, CD31 and Ki67.

Conclusion: Tumor growth of different human colorectal cell lines could be monitored by non invasive Bioluminescence imaging as well as endoscopy. Our new established orthotopic CRC tumor model in the colon descendence now provides the basis for further pre-clinical studies to validate new contrast agents and new therapy targets to obtain clinically relevant data.

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Rac1 is a therapeutic target for pancreatic cancer prevention and treatment

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Pancreatic cancer reveals very high mortality rates due to the late diagnosis, the early metastatic spread and the lack of efficient therapies. Thus, elucidation of pancreatic carcinogenesis as well as development of new treatment strategies are urgent goals. We established several conditional mouse model of Pancreatic Ductal Adenocarcimoma (PDAC), using frequent genetic alterations found in human PDAC: activation of oncogenic $Kras^{G12D}$ and EGFR signaling together with inactivation of tumor suppressor p53. These mice show complete spectrum of clinically relevant preneoplastic lesions: PanIN and IPMN, which progress to invasive and metastatic PDAC. RAS-related C3 botulinum substrate 1 (Rac1) is a Ras- and EGFR-effector molecule. Rac1 is up regulated in several human cancers including PDAC and is known to control cellular motility, proliferation and survival. The aim of this study was to investigate the role of Rac1 in the development of PDAC and its possible application as a therapeutic target.

$Kras^{G12D/+}$(K), Ela-Tgfa (T), and $p53^{R172/+}$ (P) mouse models were crossed with $Ptf1a^{+/Cre}$ and $Rac1^{fl/fl}$ (R) mice. The tumor onset and progression in the resulting pairs of mouse models (wt-R; K-KR; KT-KTR; KP-KPR) were histologically characterized as well as with ex vivo acinar transplants, Western blot, expression microarrays, RT-PCR and survival analysis.

Rac1 m-RNA and protein levels were up regulated in all analyzed mouse models (K, KT) of PDAC. Deletion of Rac1 in these models led to a strong impairment of PanIN and IPMN (KTR) development as well as a reduction of inflammatory infiltrates, desmoplastic stroma formation and cytokine secretion in KR and KPR models. In addition, acinar epithelial explants lacking Rac1 were unable to undergo Acinar to Ductal Metaplasia (ADM) in 3D cultures after TGFa stimulation. ADM of wild-type acini was similarly impaired after treatment with inhibitors of actin polymerization, supporting a potential role of Rac1 in actin-dependent plasticity during ADM. Furthermore, treatment of primary mouse tumor cell lines with the Rac1-specific inhibitor NSC23766 in vitro resulted in a strong negative effect on adherent and anchorage-independent cell growth.

In conclusion, we show that Rac1 is essential for ADM and development of preneoplastic lesions in several mouse models of PDAC and propose Rac1 as a new target for prevention and treatment of PDAC.