dependent invasion is probably mediated by EGFR dependent signalling pathways.

Together, results demonstrate a role of extracellular matrix proteins in the progression of cervix carcinoma. Additionally, Siha and HeLa can be an effective *in-vitro* models for an overview of the processes involved in cervical cancer progression.

Poster Presentation: Translational Research Biomarkers

PO-471 CIRCULAR RNA DETECTION IN MELANOMA PATIENTS' PLASMA

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Introduction Melanoma is an aggressive disease, curable by surgical resection if caught at an early stage (>95% 5 year survival) but with a poor prognostic outcome when diagnosed at advanced metastatic stage (<5% 5 year survival). Therefore, there is an urgent need for biomarkers of early diagnosis. In this respect, liquid biopsies hold great promise as they are fast, non-invasive and allow repeated sampling and monitorisation of patient response.

Circular RNAs (circRNAs) are covalently closed RNA molecules that much more stable than linear RNAs to the high level of RNase activity in blood, and therefore have great potential as circulating biomarkers for cancer patient management. We therefore set out to identify and validate potential biomarker circRNAs from the plasma of melanoma patients' representing differing stages of the disease, along with healthy controls.

Material and methods Next generation sequencing (RNAseq) was performed on pools of plasma from melanoma patients with stages 0, I/II, III or IV disease, as well as healthy individuals. Back-spliced junction reads were mapped using a combination of TopHat and TopHat-Fusion, and differential expression analysis carried out with the DEseq algorithm. Three circRNA (CR-3320,–2465 and −1445) were selected for validation in 106 plasma samples from 84 melanoma patients and 22 healthy controls by qRT-PCR.

Results and discussions We obtained 20–30 million reads by RNAseq and identified between 120–200 circRNA species (after QC) in each sample. Of these 37 were differentially ($p<0.05$) expressed. Of the three circRNAs measured in an independent validation cohort, all were expressed at higher levels in melanoma patient samples than in controls. The highest levels were observed in stage 0 and I patients, decreasing in stage II and stage III/IV patients, probably due to treatment differences in the cohorts. The AUC values of CR-3320 and CR-2465 were 0.72 and 0.66 with a sensitivity of 53.33% and 30.77% and a specificity of 82.53% and 100%, respectively.

Conclusion This study suggests that circRNAs could represent a novel source of biomarkers for liquid biopsies for melanoma, and in all probability other cancers.

PO-472 MICRORNA AS BIOMARKERS OF RESISTANCE TO REGORAFENIB IN METASTATIC COLORECTAL CANCER PATIENT

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Introduction Regorafenib demonstrated efficacy in pre-treated metastatic colorectal cancer (mCRC) patients. Limited clinical benefit in unselected patient populations highlights the unmet need for better patient selection and identification of mechanisms of action. MicroRNAs (miRs) are small non-coding RNAs involved in cell homeostasis, carcinogenesis and control multiple oncogenic pathways. Numerous miRs deregulation in mCRC are associated with clinical outcome and cancer progression.

Material and methods We ran a translational phase II trial of regorafenib in chemo-refractory mCRC patients with biopsiable metastases. Tissue biopsies were obtained at baseline (BL), after 2 months of treatment, and at disease progression (PD). Patient Derived Organoids (PDOs) and PDO-xenotransplants were generated to study primary and acquired resistance to regorafenib. MiR profiling was performed in BL serum of all patients by NanoString nCounter platform and validated with digital droplet (dd)PCR in serum, plasma and exosomes and by *In Situ* Hybridization (ISH) in matching tissue biopsies. Fisher's exact test investigated potential associations between patient groups and categorical variables whilst t-test or non-parametric equivalent tests were used for continuous variables. Progression Free Survival (PFS) was measured from date of registration to date of first progression/relapse or death from cancer progression. Overall Survival (OS) was measured from date of randomisation to death from cancer. The Kaplan-Meier method summarised the survival estimates while the Cox proportional hazards model used to compare the survival rates between patient groups with and without adjustment for the effect of covariates.

Results and discussions MiR expression was tested in 43 BL sera. Dysregulation in 28 miRs was associated with PFS and/or OS. Among these miRs, up-regulation of miR-652–3 p and down-regulation of miR-3614–3 p was associated with worse PFS and OS. Results were validated by ddPCR on the same serum samples, and matching plasmas. ISH confirmed dysregulation of two miRs in sequential tissues biopsies, PDOs and PDO-xenotransplants of patients with primary and acquired resistance. Validation in an independent patient's cohort (n=70) is ongoing. Functional experiments to define miR-mediated resistance are ongoing.

Conclusion Circulating miR-652–3 p and miR-3614–3 p might be exploited as biomarkers for the upfront selection of patients' candidate to regorafenib treatment and might be used to track and forecast acquired resistance to treatment.