locally advanced/operable pts undergoing neoadjuvant T+D, pCR occurred more frequently in pts with a baseline HSP90 score of 3+, as compared to 2+ and 1+ (50.0% vs. 14.3% vs. none, p=0.05). These results suggest the possibility to classify HER2-positive pts into HSP90 defined subgroups and elaborate specific therapeutic strategies.

Conclusion Preclinical data indicate that constitutive HER2 activation induces HSP90 expression and HSP90 modulation influences the functional response to combined treatment. Baseline HSP90 expression may potentially represent a prerequisite of pharmacological response in HER2-addicted BC.

PO-503
THE COHESIN STROMAL ANTIGEN 1 (SA-1) MODULATES COLONIC AND COLORECTAL CANCER (CRC) STEM CELLS: MECHANISM FOR RACIAL DISPARITIES
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Introduction CRC disproportionately impacts African-Americans (incidence and mortality increased by ~25% and ~50%, respectively). While mechanisms remain unclear, Vogelstein posited that the number of stem cell divisions determine CRC risk Science 2015. CRC stem cells may impact mortality via chemoresistance. LGR5, aldehyde dehydrogenase (ALDH1a3) and DCAMKL1 are markers of both intestinal and CRC stem cells. We have noted loss of SA-1 (a chromatin remodeler) occurred during colonic field carcinogenesis was markedly accentuated in Blacks (Cancer Prev Res 2016) via specific SNPs (Neoplasia 2018). SA-1 loss was also associated with poorer CRC prognosis. We hypothesised that SA-1 loss leads to stem cell induction and hence CRC disparities.

Material and methods Rectal biopsies were obtained from endoscopically normal mucosa from ~200 patients undergoing screening colonoscopy with an IRB approved protocol. SA-1 was assessed by RT-PCR normalised to -actin. We modulated SA-1 in human CRC cell line HT29 and tested efficacy of chemotherapy 5 fluorouracil (5-FU) and oxaliplatin via annexin V apoptosis assay.

Results and discussions Adenoma-harbouring subjects had ~ 50% increase in LGR5, ALD1a3 and DCAMKL1 (p < 0.05) with concomitant suppression of SA-1. Causality was indicated by demonstrating that SiRNA SA-1 knockdowns (KD) in HT29 cells caused stem cell marker induction (LGR5 = 380%, ALD1a3 = 30% and DCAMKL1 = 85%, p < 0.05). SA-1 overexpression resulted in reciprocal effects downregulation of all 3 stem cell markers. Functionally, SA-1 KD suppressed 5-FU and oxaliplatin induced apoptosis by 56% and 72% respectively versus scramble vector (p < 0.0001). Underscoring racial disparities relevance was the observation that Blacks have a 31% greater SA1 loss vs. Whites (p < 0.0004) which mirrored a 35% higher upregulation in LGR5 and ALD1a3 (p < 0.05). CRISPR editing of RKO cells to have the SNP rs34149860 (found only in Blacks) resulted in SA1 loss (41% loss, p < 0.005) and concomitant ~ 45% LGR5 and ALD1a3 upregulation (p < 0.05).

Conclusion This novel finding that the proneoplastic effects of SA-1 loss may be transduced through intestinal/colonic stem cell (CRC incidence) and also augmenting CRC stem cells resulting in chemotherapy resistance (CRC mortality). Future studies may mitigate CRC disparities in Blacks through development of effective biomarkers and therapeutic.

PO-504
EXPEL: A NOVEL NON-DESTRUCTIVE METHOD FOR MINING SOLUBLE TUMOUR BIOMARKERS
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Introduction The search for biomarkers able to detect and evaluate disease such as cancer at an early stage, or to predict resistance and response to therapies, has been and remains a major challenge. Despite very important progresses in all fields of omics technologies, the success of discovery of clinically valuable biomarkers is surprisingly disappointing. Difficult mining of secreted proteins in biological fluids poses the first major hurdle, mainly because the concentration of interesting proteins in serum or urine is generally very low. The second key limitation in the field is the inaccessibility of tissue specimens from early lesions. Those are routinely required in their integrity for the complete histological evaluation in the clinical routine, leaving no residual material for research.

Material and methods We have developed a simple and original proximal tissue fluid mining method we named EXPEL. It enables efficient extraction of soluble biomarkers while conserving the tissue intact for subsequent pathological analysis. Importantly, the EXPEL method will not only allow the researchers to access human tissues that are very difficult to obtain, but for the first time, scientists and clinicians can share the same material for both experimental research and routine clinical analysis.

Results and discussions We hypothesised that subjecting tissue biopsies to cycles of low-pressure pulses under mild hypotonic conditions would allow a rapid extrusion of interstitial fluid containing the biomarkers of interest, while preserving the morphology and antigenicity of the sample for subsequent pathological investigation.

To test the value of the EXPEL method we have applied our procedure to a series of primary colorectal tumours (CRC) and liver metastasis samples (CRC-LM). This proof-of-principle study demonstrates the validity of EXPEL-extruded fluid as unique starting material for the most advanced OMICs methodologies such as proteomic, genomic, metabolic, while showing no disadvantage for routine clinical and pathological investigations.

Conclusion Our method enables, for the first time, both clinicians and scientists to explore identical clinical material regardless of its origin and size, which has a major positive impact on translation to the clinic.

PO-505
PROGNOSTIC IMPACT OF KRAS SPlicing IN MICROsATELLITE STABLE COLORECTAL CANCER
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Introduction Mutations in the KRAS oncogene represent one of the most common genetic alterations in colorectal cancer

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(CRC). KRAS is expressed as two transcript variants caused by alternative splicing, KRAS-4A and KRAS-4B, both of which give rise to oncogenic proteins when KRAS is mutated. While KRAS mutations are negative predictors of response to anti-EGFR therapy in metastatic disease, and shown to be associated with poor prognosis in the microsatellite stable (MSS) subtype, little is known about the clinical relevance of KRAS splice variants in CRC. Here, we evaluated the prognostic impact of KRAS splicing in relation to KRAS mutation status in primary MSS CRC.

**Material and methods** A total of 258 primary MSS CRCs and 41 normal mucosa samples from a population-representative series of patients treated at the Oslo University Hospital, were subjected to exon-resolution and splicing-sensitive expression analysis using microarrays (Affymetrix Human Transcriptome Arrays 2.0) and/or RNA sequencing (Illumina HiSeq 2500). The study was approved by the Medical and Health Research Ethics, South Eastern Norway, and written informed consent was obtained from all patients.

**Results and discussions** Analysis of the relative expression level of KRAS-4A and KRAS-4B revealed that KRAS splicing was altered in MSS CRC compared to normal colonic mucosa. There was no association between KRAS splicing and KRAS mutation status. However, gene set enrichment analysis of a KRAS activity signature revealed a mutation-dependent impact of KRAS splicing on downstream signalling, specific to the KRAS wild-type subgroup. In concordance, survival analysis of patients with stage III tumours revealed KRAS splicing to be associated with overall survival in KRAS wild-type (HR: 2.36, 95% CI: 1.07–5.18, p = 0.033), and not in KRAS mutant cases (HR: 0.69, 95% CI: 0.32–1.48, p = 0.337, P interaction test = 0.026). The prognostic association was retained in multivariable analysis including age, stage, gender and location (HR: 2.68, 95% CI: 1.18–6.09, p = 0.018), indicating KRAS splicing to be an independent prognostic marker in KRAS wild-type MSS CRC.

**Conclusion** Our results indicate that KRAS has prognostic value beyond mutation status in MSS CRC, and that the prognostic impact of KRAS splicing is specific to the clinically relevant KRAS wild-type subgroup.