indicate that genomic alterations alone cannot explain acquired platinum resistance in many cases, and emerging evidence suggests epigenetic alterations may be critical. We wish to investigate epigenetic changes that may drive platinum resistance in HGSC by treating established HGSC cell lines and patient-derived cells with pulses of carboplatin and investigating the nature, kinetics and plasticity of platinum-induced epigenetic changes.

Methodology
We will mimic, using an in vitro two-dimensional model, multiple cycles of platinum-based chemotherapy as used clinically. We will generate preliminary results from established cell lines and primary cultures. The primary cell cultures are collected from the ascites of patients with HGSC treated at Imperial College NHS Trust, London. Following validation (p53, PAX8 immunocytochemistry), carboplatin sensitivity is assessed (sulforhodamine B assay). Cells are then pulsed with four cycles of carboplatin (50μM for 6 hours) with a week of recovery between each cycle. Chemosensitivity of surviving cells is measured after each cycle. The cells are then harvested for downstream methylation (Illumina 850k array), transcriptomic (RNA sequencing) and chromatin accessibility (ATAC sequencing) assays. Cells are also imaged using STORM (Stochastic Optical Reconstruction Microscopy). Preliminary STORM data already indicate differences in chromatin structure and the distribution of specific histone modifications between paired sensitive and resistant HGSC cell lines.

Results
We will receive the raw data within 8–12 weeks from now for the bioinformatic analysis. Differential gene expression analysis will uncover differently enriched pathways under the selective pressure of platinum-based chemotherapy.

Conclusion
Understanding the epigenetic landscape of HGSC in real time using physiologically relevant models will allow us to identify possible therapeutic targets that could eventually prevent platinum resistance.

P-CADHERIN: A PROMISING PROGNOSTIC BIOMARKER FOR HOMOLOGOUS REPAIR PROFICIENT HIGH GRADE SEROUS OVARIAN CARCINOMA

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Introduction/Background
Homologous repair (HR) proficient tumours constitute 2/3 of high grade serous ovarian carcinoma (HGSC), being associated with worse prognosis. Therefore, the identification of clinically relevant biomarkers is an urgent unmet clinical need. Once classic cadherins are transmembrane glycoproteins involved in cell-cell adhesion that are frequently deregulated in cancer, we aimed to: 1) characterize the expression pattern of E-cadherin (CDH1), N-cadherin (CDH2) and P-cadherin (CDH3); 2) evaluate their prognostic impact in terms of overall survival (OS), according to HR status.

Methodology
Retrospective study using a convenience sample of archive human tissue (Fallopian tube epithelium (FTE), serous precursor lesions and chemo-naïf HGSC) from a Portuguese cancer centre. In vitro and in silico validation performed using HGSC cell lines (BG1 and OVCAR4 cell lines) and CCLE database, respectively. Protein expression evaluated using immunohistochemistry (H-scoring system) and western blot. Comparisons between groups were made using T-test and X2, where appropriate. Survival analyses were estimated using Kaplan-Meier analysis and Log-rank test.

Results
We included 321 samples (130 FTE, 53 precursor lesions and 138 HGSC; 41.2% BRCA1/2 or RAD51D mutated) from 221 patients. All HGSC co-expressed the 3 cadherins (28% with high co-expression scores). Expression pattern did not differ according to HR status. P-cadherin was significantly upregulated both in precursor lesions and HGSC, when compared with FTE. CDH3 expression was positively correlated with CDH1, EpCAM and GRHL2 and inversely correlated with VIM, both in in silico and in vitro. HGSC with high cadherin co-expression and high P-cadherin expression were significantly associated with shorter OS in the HR proficient subgroup.

Conclusion
Our results suggest that P-cadherin upregulation may be an early event in the serous carcinogenesis and a poor prognosis biomarker in HR proficient HGSC. Functional assays are currently ongoing to unravel the biological mechanisms underlying P-cadherin role in this subgroup.

ETHNICITY-SPECIFIC SPECTRUM OF BRCA1, BRCA2 AND ATM PATHOGENIC VARIANTS IN OVARIAN AND BREAST CANCER PATIENTS FROM NORTH CAUCASUS

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Introduction/Background
North Caucasus hosts several large ethnic groups, which preserved their national identity through the course of history. These populations are likely to have a unique pattern of disease-predisposing alleles reflecting the genetic background of their ancestors.

Methodology
This study involved ovarian cancer (OC) and breast cancer (BC) patients from Chechnya (n = 147), Kabardino-Balkaria (n = 139), North Ossetia (n = 83), Ingushetia (n = 88) and Dagestan (n = 137). The entire coding sequences of BRCA1, BRCA2 and ATM genes were analyzed by next-generation sequencing (NGS) in 180 OCs and 414 BCs.

Results
Consecutive OC series were characterized by high frequency of BRCA1/2 mutations across all analyzed ethnic groups, ranging from 18% to 33%. BC patients, which were enriched by early-onset, family history-positive and receptor triple-negative disease, showed mutation rate varying from 4% to 14%. There were founder pathogenic alleles in Chechens (BRCA1 c.3629_3630delAG; 10 out of 20 BRCA1/2 mutations) and North Ossetians (BRCA2 c.6341delC; 6 out 10
Circulatory HMGB-1 as a Plausible Comprehensive Assessment of Gene Mutations Revealed Overlapping Dependencies for PARPi and Chemotherapy Response in Ovarian Cancer

Introduction/Background PARP inhibitors (PARPi) have revolutionized the therapeutic landscape of epithelial ovarian cancer (EOC) prolonging the progression-free survival, especially in BRCA1/2 mutations carriers or in patients with defects in homologous recombination (HR) repair. However, it remains uncertain which PARPi to apply and how to select responders using clinical and molecular characteristics, especially in front-line therapy when platinum sensitivity is still unknown.

Methodology We selected 33 promising genes that showed a prediction of enhanced PARPi sensitivity after a systematic literature review and the exploration of publicly available CRISPR-Cas9 library screens and Genomics of Drug Sensitivity in Cancer data. We performed functional assessment in six constitutively Cas9 expressing OC cell lines and subsequently examined our set of genes using a CRISPR-Cas9 mutagenesis assay with various PARPi and carboplatin.

Results Our functional screen identified ten novel potential PARPi response biomarkers, with different impact on cell fitness and drug response. ATM was the only gene that produced an enhanced olaparib sensitivity in all the cell lines. Acquired olaparib sensitivity was also observed for MUS81, NBN, RAD51B/C, RNAEH2A, PALB2, XRCC1, and XRCC3 in at least 3 cell lines. CDK12 was identified as an essential gene in all the cell lines tested without altering the response to Olaparib. Since the best clinical biomarker of PARPi sensitivity remains the sensitivity to chemotherapy, we next compared dropout rates of top candidate genes under different PARPi (olaparib, niraparib, talazoparib) and carboplatin. Interestingly, we observed almost identical results, independently of tested gene and drug compound. This confirming the strong correlation of cancer cell response to DNA damaging drugs.

Conclusion Our data show various overlapping gene dependencies suggesting a general mechanism-of-action of PARPi and chemotherapy. Genetic screen of the identified set of genes correlated with PARPi sensitivity may allow a better stratification of patients with increase benefit to this treatment.