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**EX VIVO PROSTATE CANCER CULTURE SYSTEM Recapitulates in Vivo Response to Androgen Antagonist**

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Introduction In *ex vivo* models of prostate cancer (PCa) do not always accurately represent the different stages of PCa nor reliably predict treatment efficacy. Therefore, we have developed an experimental platform in which we cultured tumour slices from patient-derived prostate cancer xenografts (PDX) and tested whether *ex vivo* PCa culture can recapitulate the *in vivo* response to the androgen antagonist enzalutamide.

Material and methods In this *ex vivo* PDX culture system we used tumours from two PCa models in mice, one androgen receptor (AR) expressing model and one AR-negative model. Tumours were removed from the mice and sliced using a vibratome. We characterised the tumour slices by analysing morphology, cell proliferation, apoptosis, expression levels of AR and excretion of prostate specific antigen (PSA). To test the sensitivity to androgen antagonist, tumour slices from the AD and AI models were treated with enzalutamide.

Results and discussions We optimised support materials, growth medium and use of a 3D smooth rocking platform to increase oxygen and nutrient exchange. Under optimal condition, the tissue slice cultures maintained morphology, proliferative capacity and viability for at least six days. AR expression was largely maintained and tumour slices continued to secrete PSA in *ex vivo* expressing tumour slices and responded to enzalutamide with a significant decrease of S-phase cells, increase of apoptotic cells, dramatic reduction of AR expression and inhibition of PSA secretion. As expected, the AR-negative model did not respond to the AR antagonist.

Conclusion This thorough characterisation of PCa PDX tumour slices in an *ex vivo* culture system showed that the response to enzalutamide recapitulates that observed *in vivo*. The faithful retention of tissue structure and function in this *ex vivo* model offers an ideal opportunity for drug screenings, thereby reducing costs and numbers of experimental animals.

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**IN VITRO CLINICAL TRIAL FOR Pancreatic CANCER PATIENTS**

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Introduction Drug treatment response prediction for cancer patients is still a challenge. It compromises clinical trials due to suboptimal selection of patients and leads to disappointing response rates for drug treatment in the clinic. Functional testing using 3D cultures of patient tumour biopsies offers the opportunity to test drug sensitivity upfront, and subsequently optimise treatment strategies for patients. Our technology based on 3D image analysis of tumour cultures accommodates accurate evaluation of drug sensitivity with small amounts of heterogeneous tumour samples. We have initiated a clinical trial to compare drug sensitivity of tumour cultures from pancreatic cancer patients, and clinical response on standard of care treatment.

Material and methods 3D cultures embedded in an extracellular matrix protein hydrogel are generated from tumour tissue of pancreatic cancer patients and exposed to standard-of-care therapies including FOLFIRINOX (combination of fluorouracil, oxaliplatin, irinotecan) and gemcitabine. An automated high content screening platform measures morphologic features of the tissue, cells and nuclei. Drug responses are reported by parameters such as tumour cell death, apoptosis, growth arrest, and local invasion. In addition, genetic characterisation of the tumour will allow further identification of relevant biomarkers. Advanced bio-informatic analysis will establish the correlation between drug sensitivity of tumour cultures with treatment response in the clinic.

Results and discussions We present interim results of the trial (approved by LUMC ethical review board) with 3D cultured tumour material from pancreatic cancer patients. Differentiated drug responses are identified for treatment schedules including standard-of-care therapies and novel drugs that are not (yet) considered standard of care (targeting Wnt signalling pathway, PARP inhibitors).

Conclusion Functional testing is gaining interest for the development of personalised prediction of treatment outcome. Our technology enables drug sensitivity testing with standard-of-care and novel agents in 3D tumour cultures. Patient specific treatment responses can be measured per drug. Ongoing trials will establish the correlation with treatment response in the clinic. Our study results could accelerate (pre) clinical development of novel drugs. In addition, it offers opportunities to develop predictive testing for patients that are candidates for clinical trials, and to improve selection of existing drug treatment options for patients in the clinic.

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**THE EMERGING ROLE OF Junctional Adhesion MOLECULE-A (JAM-A) AS A NOVEL DRUG TARGET IN DUCTAL CARCINOMA IN SITU (DCIS)**

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Introduction Junctional Adhesion Molecule-A (JAM-A) is a cell-cell adhesion protein whose increased expression is associated with poor prognosis in patients with invasive breast cancer. However little is known about its potential role in early breast cancer, specifically ductal carcinoma in situ (DCIS). We investigated whether JAM-A is overexpressed in DCIS patient tissues, and whether its pharmacological antagonism using a novel inhibitor of JAM-A signalling, termed JBS-2, utilising *in vitro* and *in vivo* models of DCIS could reduce functional behaviours associated with tumorigenicity.

Material and methods A patient tissue microarray (TMA) comprising DCIS samples (n=50) and normal adjacent tissue (NAT) (n=26) was stained for JAM-A and semi-quantitatively scored. Using a HER2/JAM-positive cell line model of DCIS, SUM-225 and an *ex vivo* primary DCIS breast culture, we...
investigated cell viability following pharmacological targeting of JAM-A and HER2/EGFR. The tolerability of JBS-2 in vivo was examined in NOD-SCID mice via intraperitoneal injection for 14 days. Finally, JBS-2 was tested for anti-tumorigenic effects alone or in combination with the HER2/EGFR tyrosine kinase inhibitor lapatinib in an in vivo mouse model of breast cancer following SUM-225 cell implantation in the mammary fat pad of NOD-SCID mice.

Results and discussions Immunohistochemical analysis revealed 96% of DCIS tissues had moderate/high JAM-A expression in comparison to 23% of NAT. Treatment of SUM-225 cells with JBS-2 or lapatinib significantly inhibited cell viability in a concentration-dependent manner. Co-treatment of SUM-225 cells with JBS-2 and lapatinib additively inhibited cell viability over either treatment alone. JBS-2 also reduced cell viability on an ex vivo DCIS primary culture. NOD-SCID mice treated with JBS-2 for 14 days revealed no haematological, biochemical or histopathological toxicity. Importantly, in a SUM-225 orthotopic murine model of DCIS, treatment with JBS-2, either alone or in combination with lapatinib, significantly inhibited tumour progression. JAM-A staining of SUM-225 tumours following treatment revealed those treated with JBS-2 had a 30% reduction in JAM-A expression in comparison to the control.

Conclusion The role of JAM-A in DCIS is unknown. Increased expression of JAM-A in DCIS tissues coupled with the responsiveness of a HER2-positive DCIS model to a JAM-A inhibitor suggests novel potential in investigating JAM-A inhibitors alone or in combination with HER2 inhibitors as preventative or therapeutic agents in this setting.

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**THE PHENOTYPIC PLASTICITY OF CASTRATION-RESISTANT PROSTATE CANCER: FROM CHALLENGE TO OPPORTUNITY**

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Introduction We have previously reported on the development of two in vitro models (PDB and MDB) of castration-resistant prostate cancer (CRPC) (Ferrari et al. Cell Comm Sign. 2017 8:15;1). These cell lines are resistant to bicalutamide (BIC) and mimic effectively intermediate phases of CRPC. We investigated the effects of enzalutamide (ENZ) and docetaxel (DOC) on PDB and MDB and we assessed the prostate-specific antigen (PSA) and androgen receptor (AR) expression, during BIC treatment and after BIC discontinuation or exposure to 5-α-dihydrotestosterone (DHT).

Material and methods The proliferative activity of PDB and MDB was assessed using the crystal violet assay at baseline (PDB control: 10 mM of BIC and 0.1 mM of DHT; MDB control: 10 mM of BIC), after BIC discontinuation and after DHT exposure (0.1 mM, MDB only). Cell proliferation and viability were also assessed at the same conditions after exposure to ENZ (1 μM) or to DOC (0.1 mM). Western blot analysis of PSA and AR expression was performed using anti-AR and anti-PSA antibodies. Two-tailed Student’s t-test was used to calculate the p-values.

Results and discussions After BIC discontinuation, DHT administration increased significantly the growth of the highly aggressive MDB cells and conferred them sensitivity to DOC. Under any condition, ENZ showed agonistic properties on MDB, rather than cytotoxic effects. The less aggressive PDB cells showed sensitivity to both DOC and ENZ during BIC administration, but not after BIC discontinuation. AR variants were not detected in our cell lines. AR and PSA showed dynamic expression, depending on type of cell line and BIC or DHT exposure. AR expression was not associated with PSA expression or with cell growth. The heterogeneous response of MDB and PDB to both DOC and ENZ properly mimics the variable response, observed in patients with CRPC, to hormonal and chemotherapeutic agents. Our results indicate that plasticity and rapid metabolic adaption contribute to CRPC cells survival in an androgen-deprived environment. Our preclinical evidences also suggest that androgen and antiandrogen administration might modulate AR activity and resistance to therapies in CRPC.

Conclusion We demonstrated that AR and PSA expression are dynamic in antiandrogen-resistant cells and that response to both DOC and ENZA may depend on first-line antiandrogen and/or androgen administration. Further studies should investigate the molecular mechanisms underlying these findings.

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**TARGETING CO-REGULATORS OF HORMONE-RECEPTORS AS A NOVEL THERAPEUTIC APPROACH FOR PROSTATE AND BREAST CANCER**

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Introduction Current treatments for prostate cancer mainly target the Androgen Receptor (AR), however despite an initial response these treatments fail. Among the multiple mechanisms of resistance, aberrations in AR co-factors and co-regulators represent a promising therapeutic approach since co-factors and co-regulators are not susceptible to AR resistance mechanisms. Triple negative breast cancer (TNBC) is an aggressive form of breast cancer (BC) which lacks oestrogen receptor, progesterone receptor, and HER2 amplification. Due to the fact that a proportion of TNBC express AR and that AR expression has been associated with poor prognosis, targeting AR in TNBC is attracting increasing interest. We previously identified Serum Response Factor (SRF) as an important transcription factor in an in vitro model of castrate-resistant prostate cancer (CRPC). We showed SRF association with CRPC and survival using TMAs of CRPC tissues. A cross-talk between AR and SRF in vitro and in clinical samples was also demonstrated. Using the SRF inhibitor CCG1423, we showed that combination of CCG1423 and Enzalutamide, a new-generation AR-targeting agent, is significantly more effective than monotherapies. The aim of this study was to extend our discoveries from prostate to breast cancer.

Material and methods Three TNBC cell lines with different expression levels of SRF and AR were selected to investigate the effect of SRF inhibition on cell viability and migration. CCG1423 was used to inhibit SRF. Cell viability was assessed by