Tissue Slice Culture: An ex-vivo tumour culture platform for pharmacodynamic analysis and dose response readouts

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Introduction

• The majority of preclinical oncology drug development involves the use of reductionist 2-dimensional in vitro culture and xenograft tumour models.

• Drug failures in the clinic may in part be due to the fact that these preclinical models do not represent the complexity (heterogeneity) that is observed in human tumours. The PREDECT1 consortium has been established to develop complex preclinical models for common solid tumours for target validation.

Methods: Tissue Slice Culture

• Xenografted MCF-7 tumours were harvested and 250µm tissue slices were generated using a Leica VT1200S vibrating microtome.

• Slices were cultured with or without a nitrocellulose culture support in phenol red free DMEM/10% FCS/5% L-Glutamine/5% PenStrep at 37°C, 5% CO2.

• IHC was carried out for various biomarkers of interest. Analysis of IHC images was carried out using Aperio image analysis software.

1. Culture supports improve the reproducibility of slice morphology

2. Slices in unsupported culture lose E-cadherin expression and the presence of macrophages

3. Culture at an air-liquid interface allows retention of ERα positivity and introduces heterogeneity to the tumour tissue

4. Fulvestrant (Faslodex) reduces ERα and Ki67 expression in a time and dose dependent manner

Conclusions

• Xenografted MCF-7 tumours can be cultured for up to 72h ex vivo, and retain a similar 3D architecture, biomarker expression and stromal microenvironment to that observed in vivo.

• Functional pathways were able to be modulated in these slices, and changes were observed in downstream biomarkers indicating a response to therapy.

• This culture platform could be useful in determining feedback loops and resistance mechanisms in a 3D environment, more similar to the in vivo situation.