

Human mesothelioma cell lines developed from malignant pleural effusions as tools to develop novel therapies and guide personalised medicine

Kanellakis NI, Asciak R, Yao X, Peng Y, Mercer R, Sherrill TP, Maldonado F, Ebner D, Seymour LW, Rintoul RC, Blackwell TS, Stathopoulos GT, Dong T, Rahman NM and Psallidas I

Background: Mesothelioma is an aggressive and incurable malignancy which typically presents with malignant pleural effusion (MPE) and is strongly associated with shortened life expectancy and compromised quality of life. Management of MPE remains symptomatic and current mesothelioma chemotherapy regimens only prolong survival by approximately 10 weeks. The development of novel treatments and translational models to improve patients' management are desperately needed.

Aim: To develop a panel of human mesothelioma cell lines suitable for high-throughput drug screening and discovery of novel therapies.

Methods: MPE samples from patients with mesothelioma who underwent pleural fluid aspiration were collected and cultured for at least 20 passages to establish a pure cancer cell population. The cells were grown until 70-80% confluency before passaging. Between every passage a proportion of the cells was frozen and kept as a backup to cross-examine the genetic profile. T-cells from the MPEs were isolated and cultured to examine the potency of anticancer immunotherapies. To enrich our panel, early passage primary cells derived from pleural biopsies (Mesobank, UK) were grown to pure cancer cell lines.

Results: We established a panel of 30 primary personalised mesothelioma cell (PMC) lines, with a success rate of 65% (30/48). The cells were immortal, exhibited colony formation, pale cytoplasm and nuclear atypia. An anticancer drug library was used to perform a preliminary high-throughput drug screening assay on 3 of the PMC lines (Figure 1). Cell viability was measured 48 hours post treatment and each agent's response was compared to pemetrexed/cisplatin (z-score). Average Z-Factor for responsive cell lines was 0.6 suggesting the screen performed as expected. Results demonstrated the heterogeneous drug response between different patients. T-cells

were successfully cultured from MPEs with a potential to examine T-cell antigen specific treatments.

Conclusions: We designed and developed a methodology to establish patient derived mesothelioma cell lines that can be used as tools for the discovery of novel treatments and to refine management.

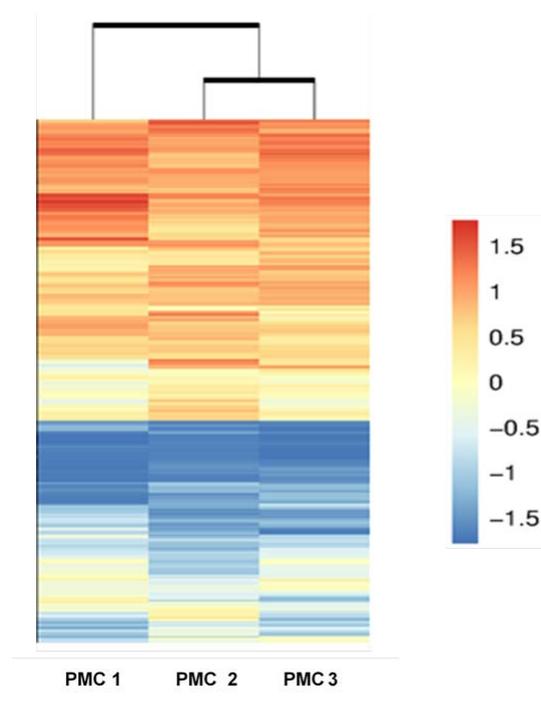


Figure 1: Heatmap of unsupervised hierarchical clustering of the drug response. Each column represents an PMC line and each row a drug. The colours represent the cell viability Z scores. Far red represents maximal viability (no drug response), while dark blue represents best drug response. There is an interpatient heterogeneous response to anticancer drugs.