

# Cancer Research

Experimental and Molecular Therapeutics

## Abstract 2072: Combination of CDODA-Me, a glycyrrhetic acid derivative, and Erlotinib overcomes chemo-resistance in NSCLC PDX spheroids and 3D bio-printed cells

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### Abstract

Patient-derived Xenografts (PDXs) are considered as relevant preclinical model for anticancer drug development due to original recapitulation of patient genetic profile, gene expression patterns and tissue histology. In this study, we investigated combination efficacy of CDODA-Me (Methyl 2-cyano-3,11-dioxo-18-olean-1,12-dien-30-oate) and TKI inhibitor Erlotinib (ERL) against Lung NSCLC PDX spheroids and 3D bio-printed PDX cells. NSCLC PDX cells (EGFR T790M mutants) were obtained from Dr. Rishi's Laboratory. PDX spheroids were grown in DMEM/ F12 media supplemented with L-glutamine, B27 supplement, recombinant human epidermal growth factor (EGF) and recombinant human basic fibroblast growth factor (bFGF). Spheroids were treated with CDODA-Me, ERL alone and in combination. Cell viability was measured by MTT assay. Western blot analysis was used to study the modulation of Bcl-xL, MDR1 and ABCG2 in treated PDX spheroids. For 3D bio-printing of PDX cells, hydrogels were prepared by partial cross-linking of sodium alginate (4.5% w/v) and gelatin (1% w/v) mixture with 40mM CaCl<sub>2</sub> solution. PDX Cells were mixed with partially cross-linked hydrogel and printed with Inkredible 3D bio-printer (CELLINK, Sweden). Bio-printed scaffolds were fully cross-linked by 160 mM CaCl<sub>2</sub> solution and then incubated overnight with cell culture media. The scaffolds were treated with CDODA-Me and ERL alone and in combination. After 48 h cell

viabilities were determined by live/dead assay using fluorescence microscopy.

MTT assay showed that approximately 65% and 74% viability was observed at 10  $\mu$ M ERL and 2.5  $\mu$ M CDODA-Me respectively. Decreased spheroid cell viability was observed in ERL and CDODA-Me combination treatment. Our western blot studies showed down-regulation of Bcl-xL, MDR1 and ABCG2 in combination group. Further,  $81.04 \pm 5.65$ ,  $78.65 \pm 3.98$  and  $74.35 \pm 4.24$  percent viable PDX cells were observed in the bio-printed scaffolds after 48, 72 and 96 h respectively. Higher percentage of dead cells ( $52.62 \pm 1.66$ ) were found in the combination group than CDODA-Me ( $28.39 \pm 1.60$ ) and ERL ( $29.62 \pm 4.91$ ) alone.

In conclusion, CDODA-Me in combination with ERL was found to be effective against human lung PDX spheroids and bio-printed PDX cells by decreasing the cell viability and overcoming drug resistance. Partially cross-linked sodium alginate-gelatin hydrogel enhances the possibility of PDX cell bio-printing with high cell survival rate. CDODA-Me can be considered as an effective neo-adjuvant to improve ERL efficacy in human NSCLC.

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