

Abstract S127 Table 1. Apoptosis induced by recombinant TRAIL and MSC-TRAIL on combination with Vorinostat

	rTRAIL	Vorinostat	rTRAIL and Vorinostat	MSC-TRAIL not activated	MSC-TRAIL Activated	MSC-TRAIL not Activated + Vorinostat	MSC-TRAIL Activated + Vorinostat
Ju77	7.71%	51.35%	80.77%	10.32%	48.73%	47.44%	77.7%
CRL2081	56.75%	78.95%	96.6%	37.3%	57.63%	81.45%	90.93%
One58	13.41%	43.97%	79.27%	10.88%	53.8%	49.25%	77.8%

MPM cells are treated with recombinant Trail (100ng/ml) and Vorinostat (2.5 M). MSC are plated in 1:1 ratio with tumour cells. MSC are activated with doxycycline to induce TRAIL expression.

Introduction Malignant pleural mesothelioma (MPM) is a highly aggressive, incurable, chemoresistant tumour. Recent studies have shown that Mesenchymal stem cells (MSC) can home to and incorporate into the tumour stroma. Their tumour tropism can be used to deliver Tumour necrosis factor related apoptosis inducing ligand (TRAIL), a transmembrane protein that selectively induces apoptosis in transformed cells. However, not all tumours are sensitive to TRAIL. TRAIL works through triggering the extrinsic apoptotic pathway while conventional chemotherapeutic agents act by triggering the intrinsic apoptotic pathway. We hypothesised the crosstalk between these two pathways could be exploited by combining chemotherapy and MSC-TRAIL in MPM tumour cell lines.

Methods MSC were engineered to express TRAIL using a lentiviral plasmid vector. A Tetracycline (Tet)-inducible system was used as a backbone to control the expression of TRAIL. Apoptosis induced by recombinant TRAIL, MSC-TRAIL in MPM cell lines on combination with Vorinostat, a chemotherapeutic agent, was measured by Annexin-V/DAPI based flow cytometry.

Results The combination of recombinant TRAIL and Vorinostat act synergistically to induce apoptosis in MPM cell lines. Recombinant TRAIL and Vorinostat, as monotherapies induce 7.17% and 51.35% apoptosis in an MPM cell line JU77 respectively. In CRL2081 and ONE58 cell lines, recombinant TRAIL induces 56.75% and 13.41% apoptosis while Vorinostat leads to 78.95% and 43.97% apoptosis respectively. The combination of recombinant TRAIL and Vorinostat shows an increased amount of apoptosis in JU77, CRL2081 and ONE58 cell lines at 80.77%, 96.6% and 77.27% respectively (Table 1).

Similar synergistic affect was observed when TRAIL expressing MSCs were co-cultured with Vorinostat treated MPM cell lines. MSC-TRAIL induced apoptosis in JU77 (48.73%), CRL2081 (57.63%) and ONE58(53.8%). Combined treatment of Vorinostat and MSC-TRAIL significantly increased apoptosis to 77.7% in JU77, 90.93% in CRL2081 and 77.8% in ONE58 cells (Table 1).

Conclusion The combination of Vorinostat and recombinant TRAIL acts synergistically to induce apoptosis in malignant pleural mesothelioma cells. Similar affect is observed with the combination of MSC-TRAIL and Vorinostat. This study indicates that Mesenchymal stem cells can be used as vectors for delivery of TRAIL and upon combination with Vorinostat, could be a potential therapy for malignant pleural mesothelioma.

S128 REDUCTION OF LUNG METASTASIS BY ENGINEERED MESENCHYMAL STEM CELLS EXPRESSING SECRETED SOLUBLE TRAIL

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Bone marrow-derived mesenchymal stem cells (MSC) are promising tools for cancer therapy because they are able to

home to and incorporate within tumour tissue. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) is a pro-apoptotic protein that induces selective apoptosis of tumour cells, while sparing normal cells. Therefore it is expected that MSCs engineered to produce TRAIL would home to and kill cancer cells in a lung metastatic cancer model. Two lentiviral vectors were constructed to express the full-length (FL) TRAIL and a truncated soluble form (ILZ-sT), respectively. A secretion peptide and an isoleucine zipper (ILZ) peptide were added to the N-terminal of the soluble form to force its secreted expression and to enhance its trimerization. Human MSCs were transduced with viruses and both constructs produced soluble TRAIL into cell media that can rapidly induced apoptosis of cancer cells. However the ILZ-sT fusion construct expresses significantly higher level of soluble TRAIL, and causes better *in vitro* lung cancer cell (A549) killing than the FL one.

In coculture experiments both construct viruses transduced MSCs caused lung (A549), breast (MDAMB231), squamous (H357), and cervical (Hela) cancer cell apoptosis and death with similar efficiencies. A synergistic effect of cancer cell killing was observed for the combinational treatment of MSC-TRAIL cells with Saha, a histone deacetylase inhibitor. When systemically delivered both MSC-FLT and MSC-ILZ-sT cells showed significant reduction of lung metastasis in a pulmonary metastasis murine model. Interestingly, ILZ-sT expressing cells demonstrated higher efficiency of metastasis reduction than FLT cells. These findings suggests that TRAIL expressing MSCs particularly ILZ-sT cells could be potentially developed as a therapy for lung metastasis diseases.

S129 THE NATURAL HISTORY OF BRONCHIAL PRE-INVASIVE DISEASE

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Background Bronchial pre-invasive lesions represent the earliest stages of the stepwise progression of squamous carcinogenesis, they predominantly affect the large airways and are readily detectable using autofluorescence bronchoscopy (AFB) however very little is known about the natural history of these lesions and no randomised data exists to determine whether intervention before progression to invasion improves outcome.

Methods A total of 94 patients with bronchial dysplasia were enrolled into an on-going surveillance cohort at University College London Hospital running prospectively since 1999. Lesions were biopsied longitudinally and kept under regular surveillance with AFB and low dose annual CT scanning until resolution or progression to invasive disease occurred. Retrospective analysis of lesional destiny was undertaken to determine the proportions of progressive vs. regressive lesions that occur in low grade dysplasia (LGD- squamous metaplasia, mild and moderate dysplasia)

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