was able to significantly counteract tumor growth with a reduction of the cytokeratin-7 positive cells and by an anti-angiogenic effect. In parallel, a retrospective study on PDAC specimens form patients (n = 19) has been conducted in order to investigate TRAIL DR4, DR5 and OPG receptor expression in "real" PDAC tissue and generate insights on the possible clinical translation of our approach. Our results suggest that MSC can be vehicles for novel TRAIL variants opening novel opportunities for PDAC treatment by multiple mechanisms.

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AUTOLOGOUS MSC INFUSION IMPROVES EJECTION FRACTION AND WALL THICKNESS IN SEVERE ISCHEMIC CARDIOMYOPATHY: RESULTS FROM A CLINICAL MULTICENTRE PHASE II/III RANDOMIZED CONTROLLED TRIAL

C. Tan[1], J.E. Anderson[1], O. Maskon[2], S. Chin[3], H. Che Hassan[2], C. Choor[2], S.K. Paul[2], N. Abu Bakar[4], N. Azreen[2], N. Amran@Azman[3], Z. Ismahadi[2], L. Qizhou[5], S. Cheong[3,6], S.S. Abdul Wahid[2,7]
[1]Penang Adventist Hospital, Penang, Malaysia, [2]Cardiology Unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia, [3]Cytopeutics, Selangor, Malaysia, [4]Radiology Unit, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia, [5]Department of Medicine, The University of Hong Kong, Hong Kong, [6]Tunku Abdul Rahman University, Selangor, Malaysia, [7]Cell Therapy Center, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

Background: We have previously demonstrated that mesenchymal stromal cell (MSC) may improve cardiac function and reduce scar tissue in end-stage cardiomyopathy when administered concurrently with revascularization (either cardiac bypass operation or coronary angioplasty). In this study we compared the effects of MSC with concurrent revascularization (Group A), MSC only (Group B) and revascularization only (Group C).
Methodology: Twenty-seven patients were recruited. All patients had anterior myocardial infarction previously and baseline cardiac function (left ventricular ejection fraction, LVEF) less than 40%. Patients who were suitable for revascularization were divided into Group A or C. Patients who have had revascularization previously or were unsuitable for revascularization were allocated to receive MSC by intracoronary infusion (Group B). Patients received between 50–100 $\times 10^6$ autologous bone-marrow MSC. The LVEF, LV end diastolic diameter (LVEDD) and interventricular septum thickness (IVST) were estimated at baseline, 3 months, 6 months and 12 months follow-up. Magnitude of change in LVEF (ΔEF) was calculated as percentage of baseline value.
Results: All patients tolerated the procedure well with no proarrythmia, calcification or tumor formation. There was no difference in baseline parameters between Groups A, B and C including LVEF (27.5 ± 5.6 vs. 32.0 ± 4.5 vs. 28.0 ± 8.3%; P = 0.26). LVEF improved in all groups during follow-up. The improvements were statistically significant compared to baseline for Group B at 3 months and for Groups A and C at 6 months. The ΔEF was largest in Group A compared to Groups B and C at 12 months (130 ± 83 vs. 46 ± 37 vs. 31 ± 29%; ANOVA P = 0.02). IVST improved in Group B while LVEDD improved in Groups B and C.
Conclusions: MSC restores myocardial myocardial wall thickness and cardiac function. Concurrent MSC administration with revascularization appeared to be superior to either procedure alone for patients with ischemic cardiomyopathy.

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SYSTEMIC DELIVERY OF siRNA-BASED THERAPEUTICS USING FUNCTIONALISED SINGLE-WALLED CARBON NANOTUBES

Y. Tan[1,2], S. Cheong[2,3], C. Leong[4]
[1]Postgraduates Studies and Research, International Medical University, Bukit Jalil, Wilayah Persekutuan, Malaysia, [2]PPUKM-MAKNA Cancer Centre, Kuala Lumpur, Wilayah Persekutuan, Malaysia, [3]Faculty of Medicine and Health Sciences, University Tunku Abdul Rahman, Bandar Sungai Long, Selangor, Malaysia, [4]Center for Cancer and Stem Cell Research, International Medical University, Kuala Lumpur, Wilayah Persekutuan, Malaysia

Carbon nanotubes (CNTs) are potential candidates for drug, antigen and nucleic acid delivery vehicle in nanomedicine. The large surface of CNTs provides structural advantages and allows loading of functional groups or therapeutics such as nucleic acid, drugs and proteins. Our study is to deliver siRNA to cells using single walled carbon nanotube (SWNT) to achieve gene silencing effect. SWNT was functionalized by dissolving one mg of HiPCo® SWNTs and 5 mg of PL-PEG-NH_2 or PL-PEG-maleimide in 5 ml of water, sonicated for 60 min at room temperature and centrifuged for 6 h. The supernatant were collected and measured their concentration at 808 nm by UV–VIS–NIR spectrometer. The resulted non-covalent functionalized SWNTs were further conjugated with a 5'-thiolated siRNA against GFP (siGFP) and RFP (siRFP). *In vitro* silencing of GFP and RFP expression by SWNT-siRNA were evaluated in stable expression cell lines by fluorescence spectroscopy. A range of 50–80% GFP expression knocked down was observed in H1299, HeLa, MCF-7 and 293T cells by SWNT-siGFP. SWNT conjugated with both siGFP and siRFP were shown knocking down both GFP and RFP simultaneously in H1299 stable co-expression cell line. Also, gene silencing was observed despite incubation with inhibitors on different cellular internalization pathways. They are chlorpromazine for clathrin-mediated endocytosis inhibitor, genistein for caveolae-mediated endocytosis inhibitor and sodium azide for energy depletion agent. The successful knockdown of GFP expression in different cell lines indicated that siRNA were released from the conjugated SWNT-siRNA in the cytoplasm and silent the gene expression. It is also indicated that two different types of siRNA targets could be conjugated with SWNT and achieved two different gene silencing effects simultaneously. We also found that the internalization of SWNT by the non-phagocytic cells (H1299) did not solely depend on single cellular entry pathway to achieve the gene silencing effect.

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INTERLEUKIN-6 SILENCING IN MESENCHYMAL STROMAL CELLS BY ADENOVIRUS-BASED SHORT HAIRPIN RNA INHIBITS MULTIPLE MYELOMA CELL GROWTH

H. Teoh[1,2], P. Chong[2], M. Abdullah[2], Z. Sekawi[2], G. Tan[3], C. Leong[3], S. Cheong[1,4]
[1]PPUKM-MAKNA Cancer Centre, Cheras, Kuala Lumpur, Malaysia, [2]Faculty of Medicine & Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [3]Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, [4]Faculty of Medicine & Health Sciences, Universiti Tunku Abdul Rahman, Kajang, Selangor, Malaysia

Background: Mesenchymal stromal cells (MSC) produce high levels of interleukin-6 (IL-6) that promotes the growth of multiple myeloma. As current IL-6 monoclonal antibody therapies have yet to yield significant clinical responses, more effective method of targeting aberrant IL-6 production by MSC is needed. In this study, we evaluated the short hairpin RNA (shRNA)-mediated silencing of IL-6 in MSC and the efficacy of these modified MSC on U266 multiple myeloma cell growth inhibition *in vitro* and *in vivo*.
Methods: IL-6 shRNA adenovirus vector (pAD-BLOCK-iT/IL6), at Multiplicity of Infection of 20, was transduced into 2×10^4 MSC. Supernatant post transduction was collected at fixed intervals and IL-6 level was determined using ELISA. Viability, immunophenotypic profile and trilineage differentiation capacity of transduced MSC were then assessed. For *in vitro* efficacy assay, conditioned medium from transduced MSC were added into wells containing 3×10^2 U266 at 2:1 ratio. Viability post co-culture was determined at fixed intervals using MTS assay. The *in vivo* efficacy assay was then evaluated in a murine subcutaneous model of human multiple myeloma followed by histological analysis of the harvested tumours.
Results: At 120 h post transduction, IL-6 was suppressed to 39% at MOI = 20 when compared to control MSC (100%) without affecting MSC major biological properties. *In vitro* results showed significant inhibition of U266 cell growth by half at day 5 when cultured in conditioned medium of transduced MSC while *in vivo* results showed significant reduction of U266 tumour volume and tumour mitotic index when co-injected with transduced MSC.
Conclusion: MSC post shRNA-mediated IL-6 silencing displayed *in vitro* and *in vivo* antitumour efficacy against multiple myeloma cells. The potential of MSC for stable gene suppression using adenovirus-based shRNA transduction should be further investigated as an alternative approach for targeting IL-6 in multiple myeloma therapy.