DUAL PUNCH TUMOUR-SPECIFIC TRANSCRIPTIONAL GENE SILENCING INDUCING THERAPEUTIC APPROACH BASED ON NOVEL TUMOUR-SPECIFIC PROMOTER AND RECOMBINANT SENDAI IMMUNO-VIROSOMES

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Aim: Lack of selectivity and cell-specific delivery to malignant cells are the major obstacles for the success of cancer therapies. Treatment with current conventional modalities has reached an impasse suggesting the need for their refinement. This study therefore aims at the development of tumour-specific transcriptional gene silencing (TGS) inducing therapeutic modalities.

Methods: Placental-like alkaline phosphatase (PLAP) is ectopically expressed in a wide range of tumours and consequently its promoter is active only in such neoplastically transformed cells with little or no activity in normal cells. We used novel tumour PLAP promoter either alone or in combination with a tumour-specific enhancer system for the induction of TGS in various HPV-16-integrated cellular systems. Promoter-mediated expression of shRNA targeting the common long control region of E6/E7 imparted one level of specificity which was honed further by utilising PLAP scFv based engineered Sendai virosomes for packaging and delivery of these therapeutic constructs.

Results: Regression in expression of E6 & E7 ameliorated p53 and its target genes only in SiHa and CaSki but not in HeLa and CHO cells demonstrating the specificity of both shRNA expression as well as delivery of the cargo by recombinant virosomal vehicular traffic. TGS was induced in various in vitro models of HPV-16 by heterochromatization of the targeted region but no DNA methylation was noted. A fall in the level of an enhancer-associated transcript was observed after the shRNA treatment.

Conclusions: A combination of promoter and antibody based specificities has the potential for being developed as a possible therapeutic strategy for neoplasia.

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