

A. Scientific Abstract

Squamous cell carcinomas of the head and neck (SCCHN), unlike normal mucosal squamous epithelial cells, overexpress epidermal growth factor receptor (EGFR) mRNA and protein. EGFR protein is required to sustain the proliferation of SCCHN cells *in vitro*. To determine whether EGFR expression contributes to tumor growth, we recently demonstrated suppression of EGFR expression in tumor xenografts and inhibition of tumor growth following intratumoral administration of an antisense EGFR expression plasmid in combination with DC-chol liposomes (1 ug DNA:1 nmole DC-chol liposomes). The original U6 expression construct (pGEMmU6) was modified to introduce Xho I and Nsi I sites for convenient cloning and a 5' hairpin loop responsible for capping of the U6 RNA was eliminated using PCR-mediated deletion. A 40 base pair antisense oligonucleotide corresponding to the ATG start site of the human EGFR gene (-20 to +20) was synthesized and cloned into the Xho I and Nsi I sites of the new plasmid. Direct inoculation of this EGFR antisense construct into established SCCHN xenografts resulted in inhibition of tumor growth, suppression of EGFR expression and increased apoptosis. Sustained effects were observed for up to one year after treatments were discontinued. The EGFR antisense DNA was detected only at the injection site 7 days after a single treatment. Toxicity studies revealed no evidence of organ damage. The plasmid backbone was subsequently replaced with a previously approved vector for use in clinical trials. This phase I clinical trial is designed to determine whether interference with EGFR expression, using an intratumoral antisense-based gene therapy approach may be an effective means of treating EGFR-overexpressing tumors, including SCCHN.