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Title: Delivery of targeted chemotherapy via genetically modified microvascular flaps suppresses primary tumor growth

Introduction: Two obstacles limiting the application of gene therapy are the inability to target gene delivery and the risk of host immune response. We have previously described a technique to selectively transduce microvascular free flaps (MFF) during the *ex vivo* period. The goal of this study was to demonstrate that genetically modified MFF expressing the therapeutic transgene mIL-12 could retard local growth of a rodent breast adenocarcinoma cell line (MADB106) while minimizing systemic toxicity.

Methods: During the *ex vivo* period, MFF were perfused with either 1×10^{10} ifu of Ad.RSV-*mIL-12* (n=10) or Ad.CMV-*lacZ* vector (n=10). After reanastomosis, 1×10^{6} MADB106 cells stably transfected with β-hCG were injected subcutaneously adjacent to the flap. Postoperatively, serum was collected and analyzed for β-hCG. IL-12 expression in the flap tissue was quantified by ELISA. Tumor volume was assessed using calipers. $CD8^{+}$ immunohistologic analysis and tumor levels of IFN-gamma were quantified by ELISA to confirm the mechanism by which mIL-12 suppresses tumor growth. Systemic toxicity was evaluated by measuring liver enzyme function and by histologic examination of distant organs for inflammatory changes.

Results: Tumor volume was suppressed by 79% in rats treated with Ad.RSV-*mIL-12* as compared control rats ($P<0.05$). Differences in serum β-hCG were observed at day 9 ($p<0.001$). Tissue ELISA confirmed IL-12 expression from the flap, peri-flap tissue and pedicle. Tumors from IL-12 treated animals exhibited a heavy infiltration $CD8^{+}$ cells and showed a 4.5 fold increase in IFN-γ expression when compared to controls. There was no observed difference in liver enzymes levels and normal liver histology was preserved in the two groups.

Conclusion: This study demonstrated that MFF can be genetically modified during the *ex vivo* period to locally express chemotherapeutic proteins and suppress tumor growth while minimizing systemic toxicity. This form of "biologic brachytherapy" may provide a novel approach to target therapeutic agents to a localized area while avoiding many of the practical obstacles currently limiting gene therapy.