SYNERGISTIC EFFECTS OF MEDIATED GENE THERAPY WITH GEN2(HSV-TK) AND GEN1018(MIL-12) IN AN EXPERIMENTAL MODEL OF COLORECTAL CANCER


Background
GEN2 is a clinical-stage retrovector that integrates into rapidly dividing cancer cells and delivers an improved gain-of-function variant of herpes simplex virus thymidine kinase (HSV-TK) as a prodrug activator (‘suicide’ gene). Consequently, GEN2 induces cancer cell death upon treatment with a prodrug such as valganciclovir (VGCV). Immune cell activation can be promoted inside the tumor microenvironment (TME) by immunocytokines, such as Interleukin-12 (IL-12). IL-12 potently activates anti-tumor immune responses through enhancement of natural killer (NK) cell and CD8+ T lymphocyte cytotoxicity, but systemic administration of IL-12 has been reported to be highly toxic in clinical trials. Accordingly, we evaluated the utility of the GEN2 vector for HSV-TK suicide gene therapy combined with tumor-localized GEN1018 vector for murine IL-12 (mIL-12) immuno-gene therapy in an experimental model of colorectal cancer.

Methods
Colorectal cancer models were established in immunocompetent 8–10-week-old BALB/c mice by subcutaneous injection of 1.5 x 10^5 syngeneic CT26 colorectal cancer cells expressing luciferase as a reporter, and injected intratumorally (IT) with GEN1018(mIL-12) or GEN2(HSV-TK) for three days. In the second week, VGCV was administered by oral gavage once a day for 5 consecutive days. One of the HSV-TK/VGCV-treated groups were given additional GEN1018 (mIL-12) injections IT for an additional three days after completion of the VGCV treatments. All mice were monitored weekly by bioluminescence imaging (BLI) and measurement of tumor size, and tumor tissues were collected and harvested for analyses.

Results
Both BLI and tumor size measurements demonstrated that GEN2(HSV-TK)/VGCV suicide gene therapy in combination with a second administration of GEN1018(mIL-12) treatment could achieve enhanced long-term tumor growth inhibition, as compared to a single administration of either GEN2(HSV-TK)/VGCV or GEN1018(mIL-12) individually. Tumor growth inhibition in the combined treatment group receiving GEN2(HSV-TK)/VGCV and 2 doses of GEN1018 (mIL-12) was associated with significantly prolonged survival compared to all other treatment groups. Immunohistochemistry of tumor samples showed increased CXCL10 expression in the tumor microenvironment, associated with increased recruitment of tumor-infiltrating T cells, in groups treated with multiple doses of GEN1018(mIL-12).

Conclusions
Direct IT injections of GEN2(HSV-TK) in combination with GEN1018(mIL-12) were associated with immunomodulatory effects within the tumor microenvironment, tumor growth inhibition, and improved survival in a model of highly aggressive colorectal cancer.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0844