TGP-13 Targeting of IL-13Rα2 for the Effective Treatment of Malignant Peripheral Nerve Sheath Tumors

Oliver Mrowczynski¹, Russell Payne¹, Alexandre Bourcier¹, Christine Mau¹, Becky Slagle-Webb¹, Ganesh Shenoy¹, A.B. Madhankumar¹, Darren Wolfe², Kimberly Harbaugh¹, Elias Rizk¹, and James R. Connor¹

¹Penn State University Dept. of Neurosurgery, Milton S. Hershey Medical Center, Hershey, PA 17033 USA
²Targeted Biosciences Inc. Hershey, PA 17033 USA

**Introduction**

Malignant peripheral nerve sheath tumors (MPNSTs) are soft tissue sarcomas that arise from peripheral nerve sheaths. A target of MPNSTs is the receptor for interleukin-13 (IL-13R). IL-13R has an α1 and α2 subtype, and activation of α1 leads to caspase-3 mediated apoptosis. MPNSTs have increased expression of the α2 subtype, IL-13Rα2. IL-13Rα2 is an oncogene that acts as a decoy receptor which has a higher affinity for IL-13, allowing cancer to evade death by binding and sequestering all of the IL-13 thus inhibiting α1 activation. Decreased α1 activation enhances tumor cell survival and augments the high potential for metastasis. The subsequent increased tumorigenicity is then followed by the devastating prognosis with five year survival ranging from a dismal 15-60%. MPNSTs are currently treated with surgical resection, sometimes requiring complete limb amputation, as well as chemoradiation, all of which demonstrate limited effectiveness, and highlight the necessity for novel therapies.

The goal of this study was to demonstrate the effectiveness of intratumoral Interleukin-13 targeted pseudomonas exotoxin (IL13E13K-PE4E, TGP-13) for MPNST treatment. The upregulated IL-13Rα2 on MPNSTs provides a unique opportunity for utilizing TGP-13 to precisely target MPNSTs and cause tumor cell death. We demonstrate that TGP-13 treatment led to a significant decrease in tumor progression in vivo. IHC analysis showed increased necrosis, decreased Ki67, and increased cleaved caspase-3, supporting the in vivo findings. The intratumoral delivery and specific targeting of IL-13Rα2 also leads to a decreased side effect profile due to minimal IL-13Rα2 expression in normal tissues. The current MPNST treatment paradigm is composed of 3-prongs: surgery, chemotherapy, and radiation, all of which have been demonstrated to be unsatisfactory. This study lays the groundwork for the change of this paradigm and subsequently optimal patient outcomes by the addition of a 4th prong, intratumoral treatment with TGP-13.

**Results**

![Figure 3](image1.png)

**Figure 3.** (A) Schematic of intratumoral treatment strategy. (B) Schematic mechanism of TGP-13 within the tumor.

![Figure 4](image2.png)

**Figure 4.** (A-C) Surgical technique for orthotopic xenograft MPNST model. Sciatic nerve is isolated and microscopically injected (D,E) Visual tumor growth confirmation. (F) MRI confirmation of orthotopic xenograft MPNST model. (Red arrow denotes MPNST, blue arrow denotes the normal sciatic nerve) (G-K) STS26T cells are luciferase transfected thus able to be visualized using IVIS throughout 4 weeks of tumor development.

![Figure 5](image3.png)

**Figure 5.** In vivo tumor progression and survival. (A) Middle-Late stage MPNST mice treated with intratumoral TGP-13 (B) Survival was not significantly changed (C) Early stage tumor mice treated with TGP-13 had a significant decrease in tumor burden (D) Survival was significantly increased in the early stage treatment mice.(*p<0.05, **p<0.01)

![Figure 6](image4.png)

**Figure 6.** Blood toxicity analysis. Tests for kidney toxicity with (A-B) BUN and creatinine, as well as liver function with (C-E) alkaline phosphatase, AST, and ALT, showed no significant toxicity.

![Figure 7](image5.png)

**Figure 7.** Tumor tissue analysis (A) Visibly aberrant cellular architecture and massive necrosis in the MPNSTs treated with intratumoral TGP-13 (B) Ki67 was visibly decreased in the treated MPNSTs (C) Cleaved caspase 3 was visibly increased in the TGP-13 treated MPNSTs.

**Conclusions**

- IL-13Ra2 is robustly expressed in vitro in MPNST cells and in human sarcomas based on TCGA analysis
- TGP-13 decreases tumor burden and increases survival in an orthotopic MPNST model
- We describe a novel intratumoral treatment methodology that is able to provide treatment to all aspects of the tumor while limiting backflow

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