Treatment of Glioblastoma Through the Controlled Localized Production of IL-12 by the RheoSwitch Therapeutic System® Platform

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Abstract

Challenges in developing immunotherapies against glioblastoma include the immune-privileged state of the CNS and the immunosuppressive microenvironment that is established in the tumor. The localized controlled production of immune-stimulating cytokines could be an attractive therapeutic strategy. The RheoSwitch Therapeutic System® (RTS®) technology is a customizable transgenic expression system that allows for the controlled and localized production of therapeutic agents. This system consists of the Switch Components, the Activator Ligand, and the Inducible Promoter. The Switch Components can be used to turn on or off the transgenic expression of any gene of interest. The Activator Ligand is an agonist that binds to a switch protein and signals the fused oncoprotein to be translated resulting in effective clinical regimens for the treatment of glioblastoma.

Results (Pharmacology)

A. Dose-dependent increase in plasma exposure of Veledimex (AL) in C57BL/6 Mice

B. Dose-dependent increase in Brain Exposure of Veledimex (AL) in C57BL/6 Mice

C. Higher Veledimex (AL) Levels at 24 h in Brains of GL261 Orthotopic Glioma Mouse Model Than C57BL/6 Mice

Conclusions

• Veledimex exhibited dose-related increases in plasma and brain tissue exposure.
• Repeat veledimex dosing shows no accumulation in the brain (48 vs. 0 h).
• Influx of cytotoxic CD8+ T cells and systemic antigen presenting cells activity and T cell activation toward tumor-associated antigens, locally and systemically reduce in CD4+ regulatory T cells.
• Veledimex-induced reduction in disease progression and death was dose-related. The combination of Ad-RTS-mIL-12 + veledimex demonstrated a synergistic effect over current standards of care in the mouse orthotopic GL261 glioma model.
• Ad-RTS-mIL-12 + veledimex does not adversely affect body weight.