Inducible Gene Regulation—RheoSwitch Therapeutic System™

The RheoSwitch Therapeutic System™ (RTS™) is a three-component transcriptional regulator.

A. Dose-dependent Increase in Plasma Exposure of the Vehicle (AL) in C57B6 Mice

B. Carotid Arterial Fluid (CSF) Exposure of Veldimex (AL) in C57B6 Rats

C. Plasma Exposure of Veldimex (AL) in Cynomolgus Monkeys

D. CSF Exposure of Veldimex (AL) in Cynomolgus Monkeys

Veldimex Brain Penetration in Normal Mice and Monkeys with Intact Blood Brain Barrier

Plasma and CSF Exposures in Female C57B6 Rats

Ad-RTS-IL-12 + AL and DC-RTS-IL-12 + AL

Ad-RTS-IL-12 + AL and DC-RTS-IL-12 + AL Demonstrated Dose-Related Increase in Survival in the Mouse GL261 Glioma Model

Abstract

The challenges of developing immunotherapeutics to treat glioma include the immune-inhibited status of the C64 and the physiological processes that contribute to the suppression of immune responses in the brain. The capacity of benefitting cells (DC) in the brain combined with lack of strategic distractions, the production of anti-inflammatory mediators, and the physiological barriers provide several challenges in inducing tumor-specific responses. We have previously assessed the safety and biologic activity of two different RheoSwitch Therapeutic Systems® (RTS™) combinatorial 4-12 expression-based therapeutic candidates in Phase I clinical trials for the treatment of melanoma metastasis. Ad-RTS-IL-12 (5 x 10^9) and DC-RTS-12 (DC), along with the activator ligand vardenafil, also known as MNF-161 (AL), based upon preliminary favorable results observed for these two product candidates, we chose to study the activity of RTS-12 AL administered systemically by either a dextran coil or an abdominal vascular-based approach in an orthotopic murine glioma model. The ability of the activator AL to cross the blood brain barrier (BBB) were assessed in both C57BL/6 mice and cynomolgus monkeys. The results in mice demonstrated that the AL crosses the BBB (peak and trough levels of 17-16 mg/ml) in central spinal fluid (CSF) over the dose range of 450-900 mg/kg/day which induced tumor levels previously shown to induce the induction of IL-12 and results in a 50% tumor growth inhibition in the C64 mouse model. AL also crossed the BBB in a similar fashion in the cynomolgus monkeys. The effects of DC and AC on survival were assessed in the mouse orthotopic (C64) glioma model where each animal received 1 x 10^5 GL261 glioma cells via intracranial injection (s.c.) on Day 1. To study murine dermal cells were transduced at increasing multiplicity of infection (MOI) of 100, 500, 1,000, 5,000, or 10,000 of vector particles (vectorial). The transduced DCs were intravenously (i.v.) administered at 1 x 10^7 DC (mouse), on Day 5, AL was administered at 1 x 10^5, 5 x 10^5, or 1 x 10^6 (mouse). Survival in the mouse GL261 glioma model demonstrated dose-related increase in survival benefit without exhibiting an adverse safety profile. All animals treated with DC + 300 MOI AL or 5 x 10^5 AL survived throughout the duration of the study (100% survival at 75 days). For no adverse clinical signs observed. In contrast, the mean survival in the control groups was 20 ± 7 days. Additional studies in this model are ongoing to determine the optimal dose and schedule. This novel immunotherapeutic approach could potentially translate into an effective clinical regime for the treatment of glioma.