Intratumoral Regulated Expression of IL-12 as a Gene Therapy Approach to Treatment of Glioma

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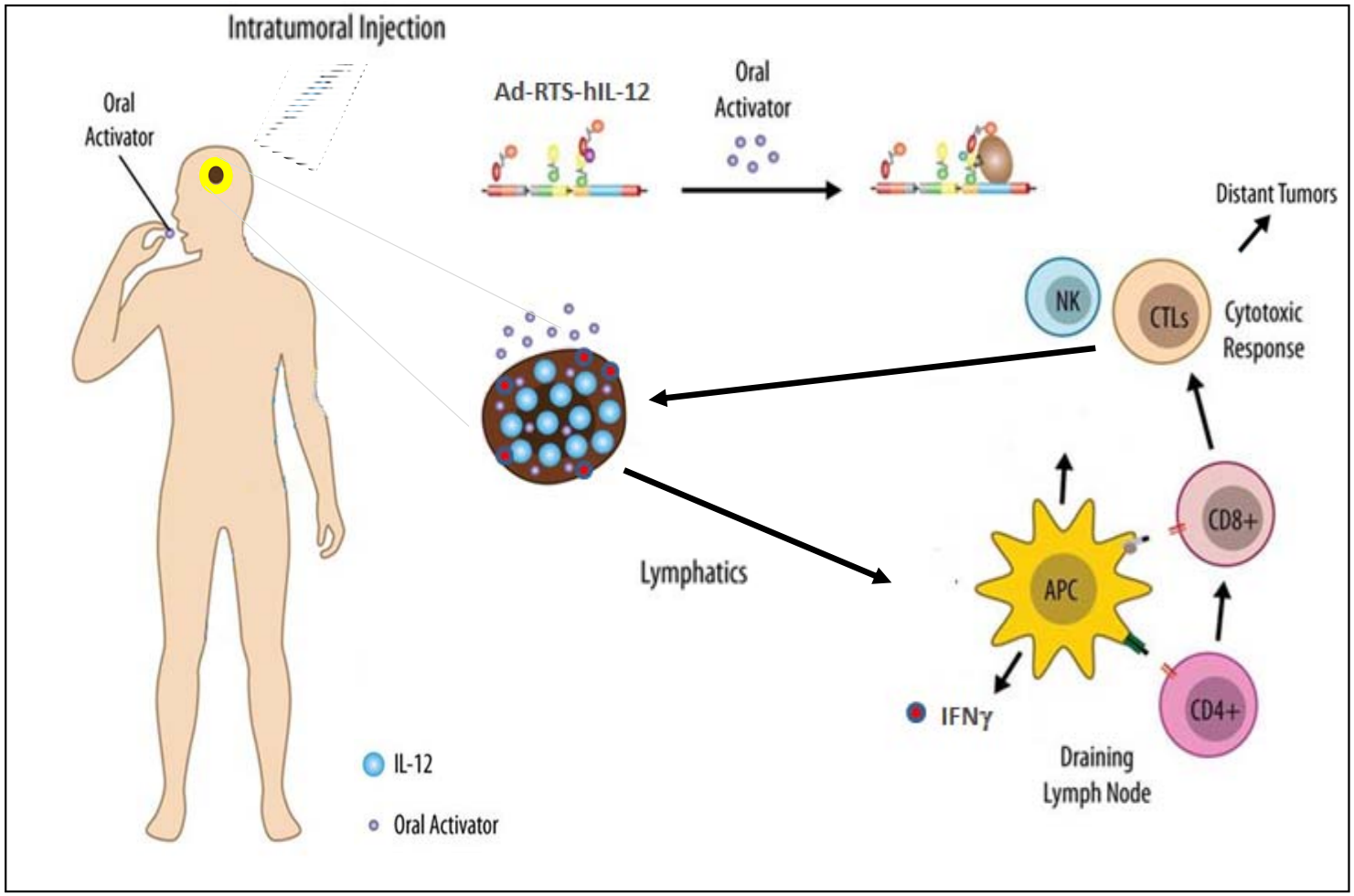


Regulated intratumoral expression of IL-12 promotes activation of tumor-infiltrating lymphocytes to drive a cytotoxic immune response

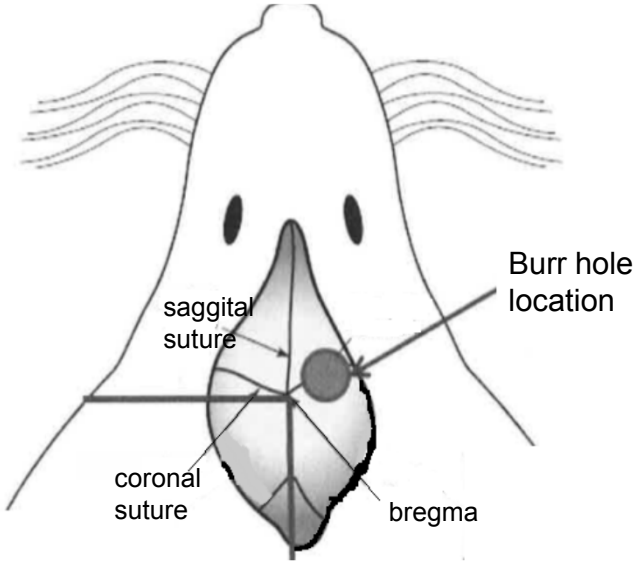
An adenoviral vector engineered to express IL-12 (Ad-RTS-hIL-12) utilizing the RheoSwitch Therapeutic System® (RTS®) gene switch is injected intratumorally

Expression of IL-12 is controlled through the administration of an oral activator ligand veledimex

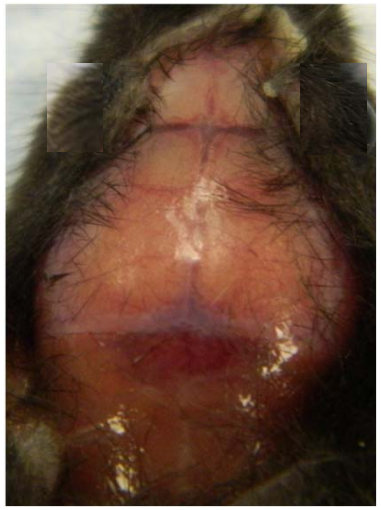
- Localized production of IL-12
- T cell activation toward tumor-associated antigens
- Influx of cytotoxic $CD8^+$ T cells coupled with a reduction in $CD4^+$ regulatory T cells

Intra-tumor injection of Ad-RTS-IL12 treats mouse glioma

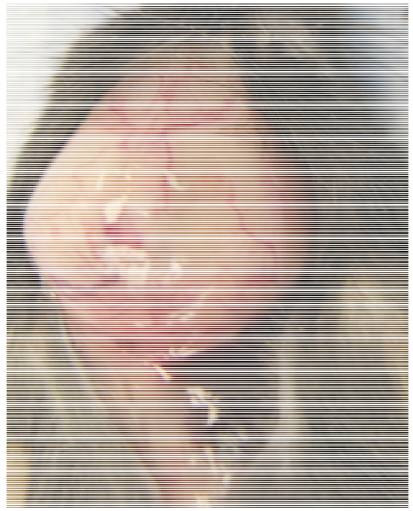
GL-261 Orthotopic Glioma Model



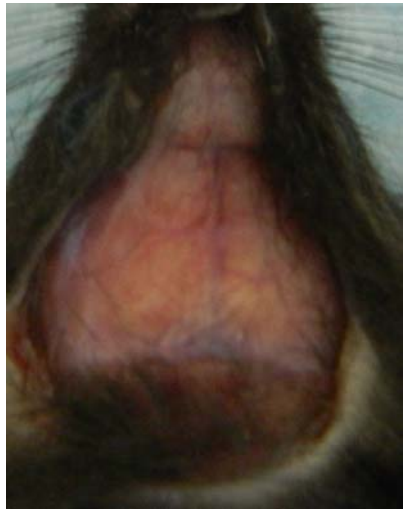
Normal Mouse



Control Day 20

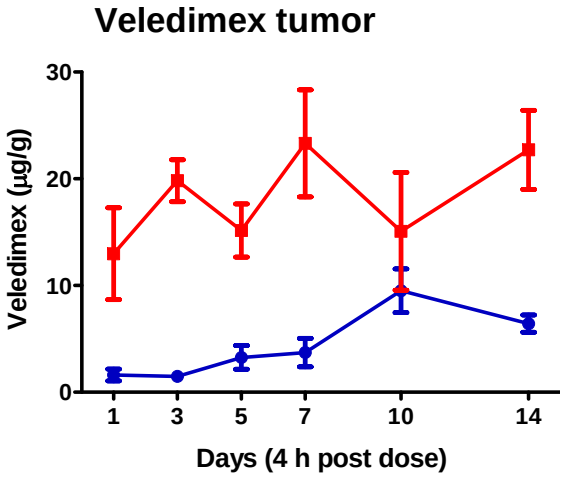


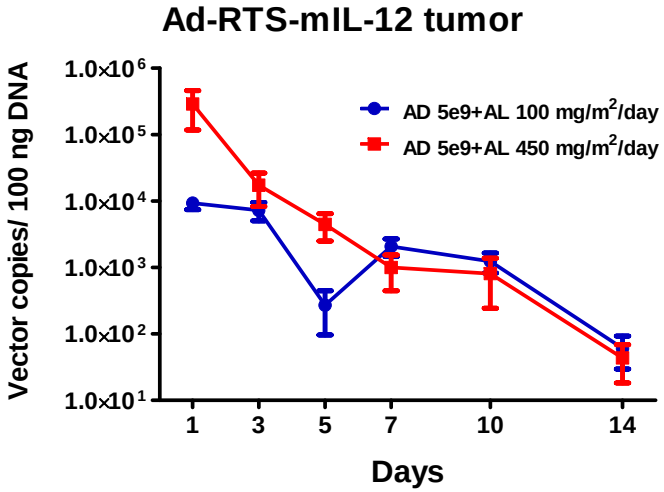
Treatment Day 74

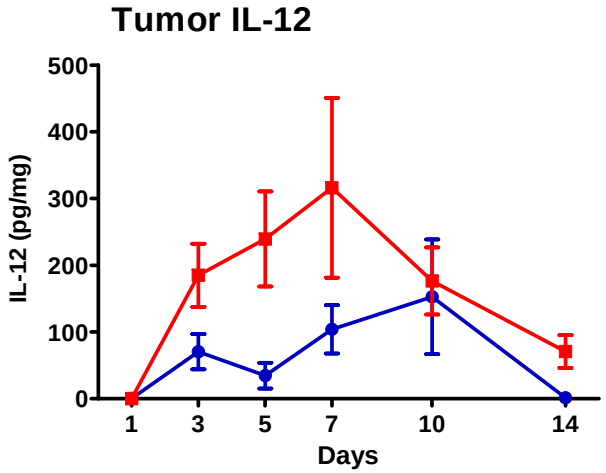


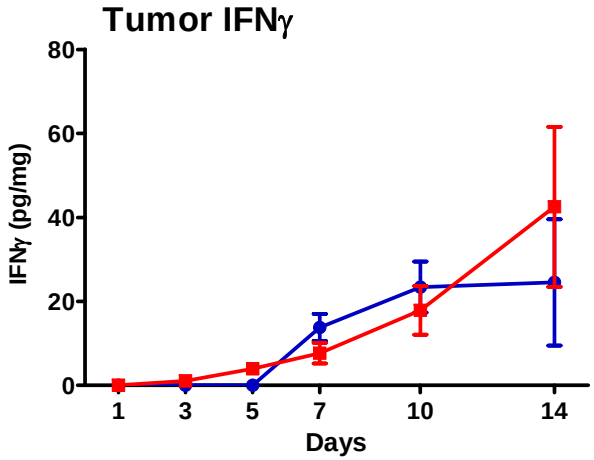
AL 450mg/m^2/day BID x14
+ Ad-RTS-mIL-12 1x10^{10}vp

Ad-RTS-mIL-12 + Veledimex is on Mechanism in GL-261 Orthotopic Glioma Model



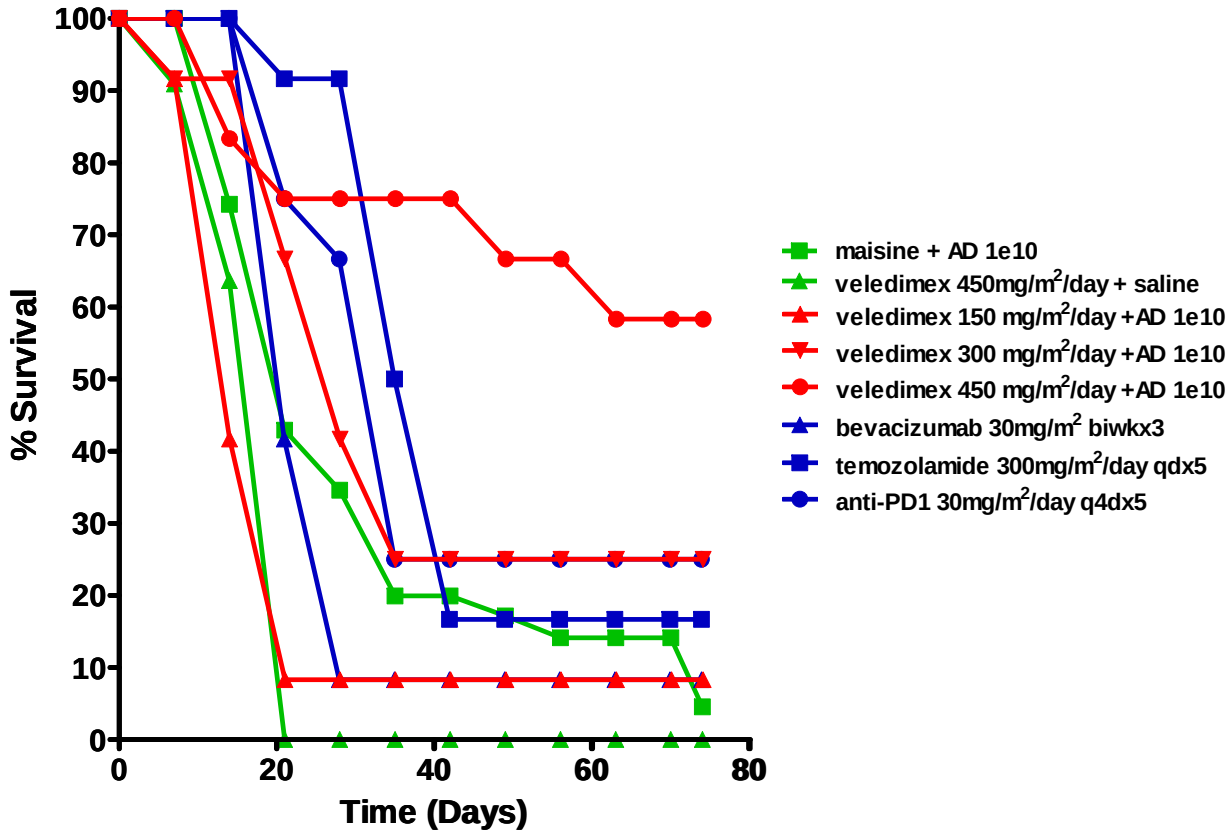




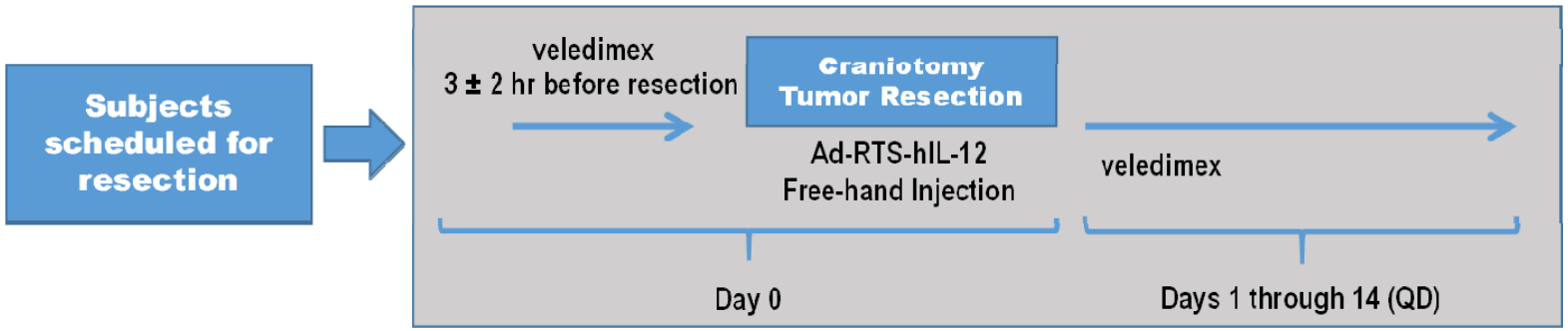


- Dose-related increase in tumor veledimex
- Tumor IL-12 correlates with vector copy, veledimex & mRNA IL-12
- Tumor IL-12 produced is biologically active
- Results indicate activation of innate immune system

Ad-RTS-mIL-12 + Veledimex Results in Increased Survival in the GL261 Orthotopic Glioma Mouse Model



Phase 1 Dose Escalation Study of Ad-RTS-hIL-12 + Veledimex in Recurrent or Progressive Glioblastoma or Grade III Malignant Glioma



Patient Demographics
N=5

Age in years Median (Min, Max)	**40 (32, 58)**
Gender Male : Female	**3 : 2**
Time Since Initial Diagnosis (months) Median (Min, Max)	**42 Months (11, 66)**
Grade at Study Entry	**Grade III 2** **Grade IV 3**

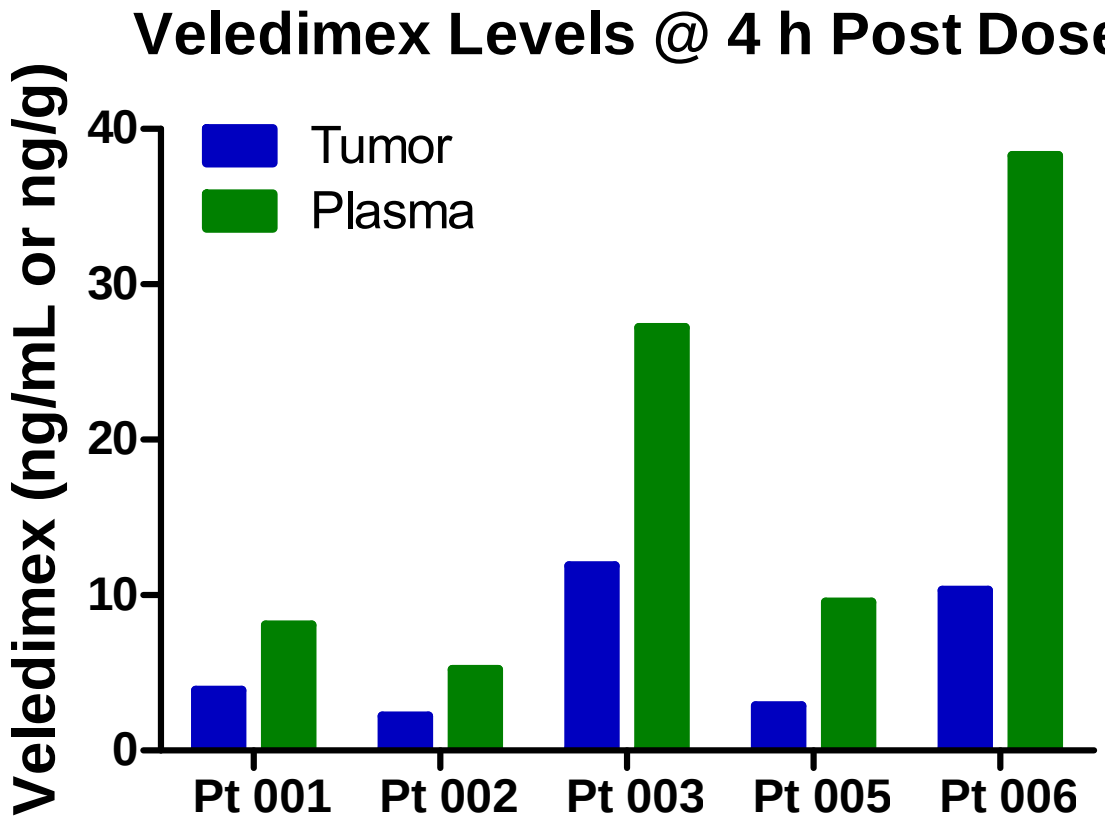
Preliminary Safety Profile
N=5

Cohort 1: Ad-RTS-hIL-12 $2x10^{11}$ vp + veledimex 20mg (10mg/m^2/day)

Most Common AEs
- Headache, Fever, Hyponatremia, Nausea/Vomiting

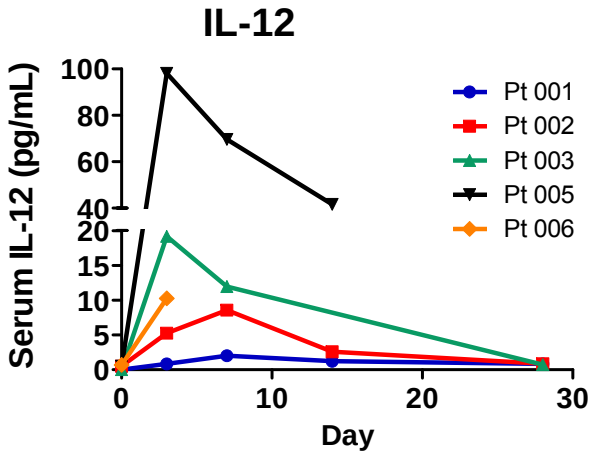
Related SAEs
- Aseptic Meningitis
- Neutropenia, Thrombocytopenia, Leukopenia

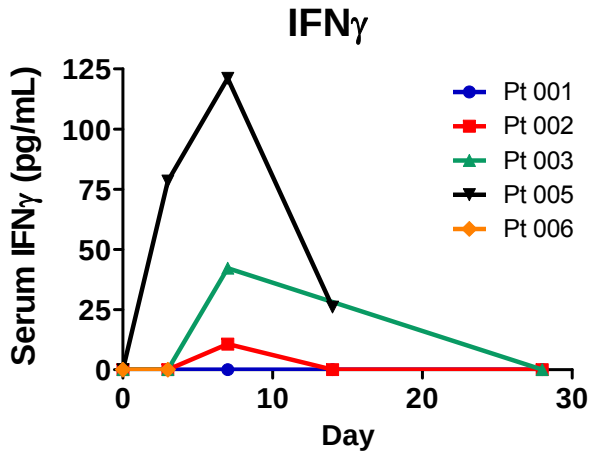
Veledimex Crosses the Blood Brain Barrier

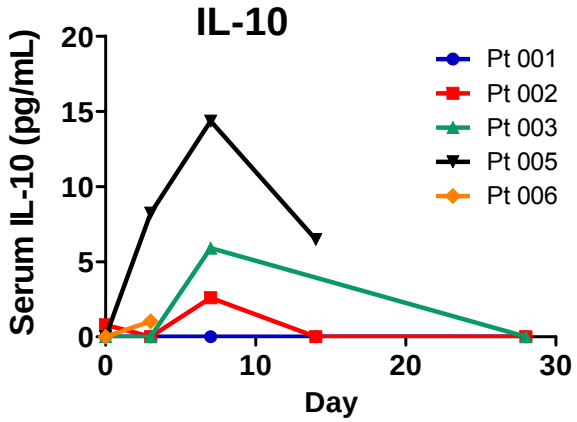


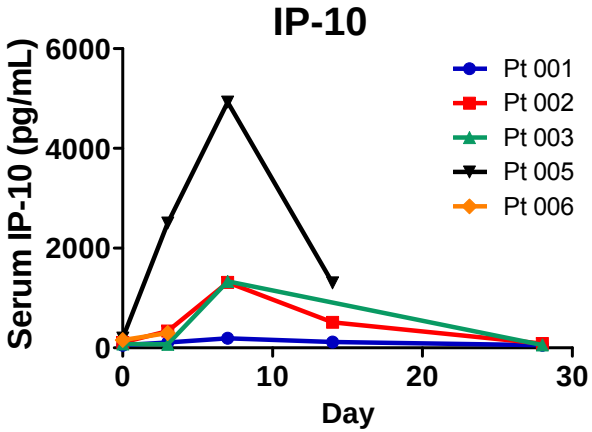
Veledimex 20 mg (10 mg/m^2/day); Pt 004 screen failure

Intra-tumor Administration of Viral Vector Activated by Veledimex Results in Functional IL-12









Veledimex 20 mg (10 mg/m^2/day);
Pt 004 not dosed

Conclusions

- Veledimex crosses the blood brain barrier
- Intra-cranial administration of Ad-RTS-hIL-12 is activated by oral veledimex
- Transcribed IL-12 peaked at Day 3 followed by downstream IFN γ
- Ad-RTS-hIL-12 + veledimex administered in patients undergoing tumor resection was well tolerated
  - Toxicity to date appears consistent with “on target” effect

IL-12 and Cancer Immunotherapy

- Interleukin-12 (IL-12)
  - Pro-inflammatory cytokine
  - Can reverse immune escape mechanisms induced by MDSCs and DCs and significantly improve the function of activated $CD8^+$ T cells resulting in the collapse of the vascularized stroma of solid tumors
  - Expression of functional IL-12 in human subjects by direct intratumoral injection of Ad-RTS-hIL-12 + oral veledimex generates downstream IFNγ production and rapid elevation of IL-10 and IP-10 in melanoma and breast cancer patients
  - We have previously demonstrated that intratumoral administration of Ad-RTS-IL-12 results in targeted tumor cytotoxicity and the induction of systemic T cell memory
  - Ad-RTS-IL-12 + veledimex explores local treatment strategy under the control of the RheoSwitch Therapeutic System® (RTS®) gene switch to extend the IL-12 therapeutic window