

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

John A. Barrett<sup>1</sup>, Hongliang Cai<sup>1</sup>, John Miao<sup>1</sup>, Margaret Murray<sup>2</sup>, Emily Gable<sup>2</sup>, Deborah Blake<sup>2</sup>, Suma Krishnan<sup>3</sup>, E. Antonio. Chiocca<sup>4</sup>, Seema Nagpal<sup>5</sup>, Jeffrey Raizer<sup>6</sup>, John Yu<sup>7</sup> and Francois Lebel<sup>1</sup>

<sup>1</sup>Ziopharm Oncology Inc., Boston, MA, United States, 02129

<sup>2</sup>Translational Drug Development, Scottsdale, AZ, United States, 85259

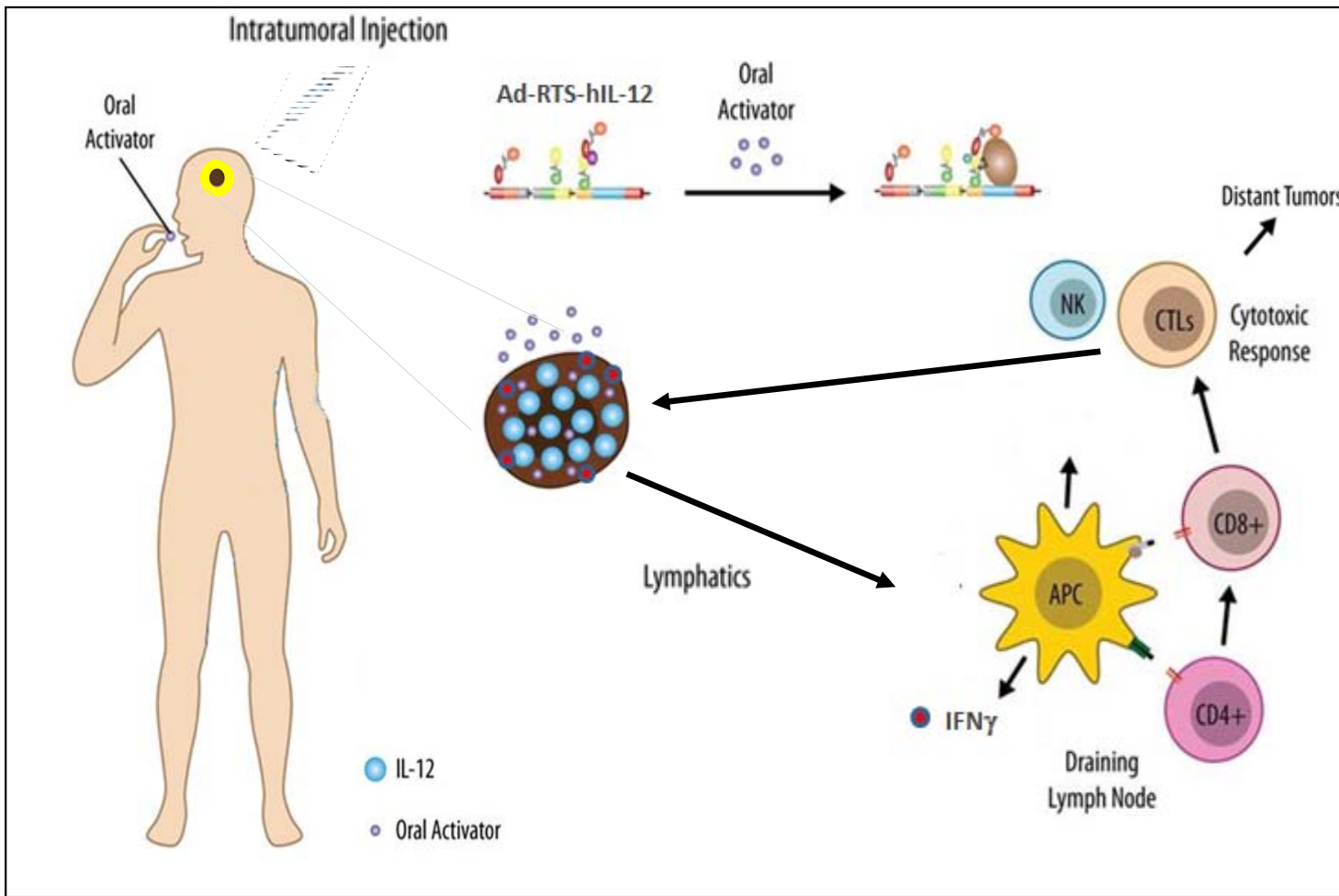
<sup>3</sup>Intrexon Corporation, Germantown, MD, United States, 20876

<sup>4</sup>Center for Neuro-Oncology Brigham & Women's Hospital, Boston, MA, United States, 02115

<sup>5</sup>Division of Neuro-Oncology Stanford University, Stanford, CA, United States, 94305

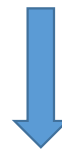
<sup>6</sup>Northwestern Brain Tumor Institute, Northwestern University, Evanston, IL, United States 60208

<sup>7</sup>Brain Tumor Center of Excellence, Cedar Sinai Hospital, Los Angeles, CA, United States 90048



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

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

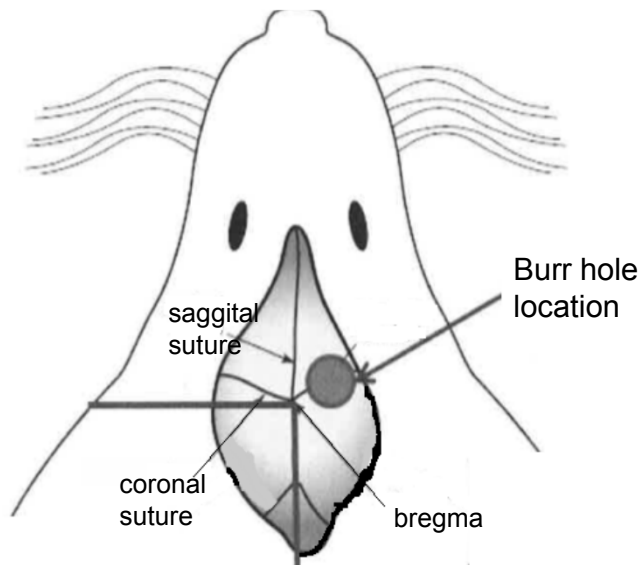


- Localized production of IL-12
- T cell activation toward tumor-associated antigens
- Influx of cytotoxic CD8<sup>+</sup> T cells coupled with a reduction in CD4<sup>+</sup> regulatory T cells

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

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

## GL-261 Orthotopic Glioma Model



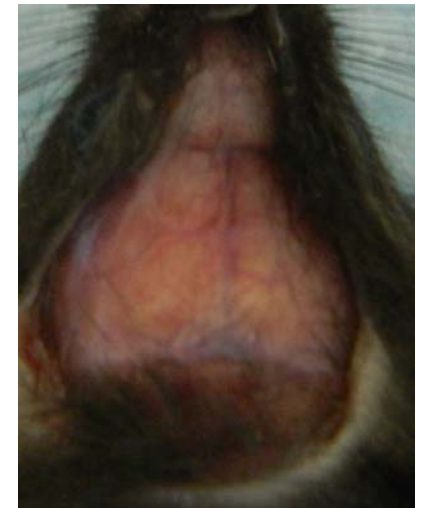
## Normal Mouse



## Control Day 20



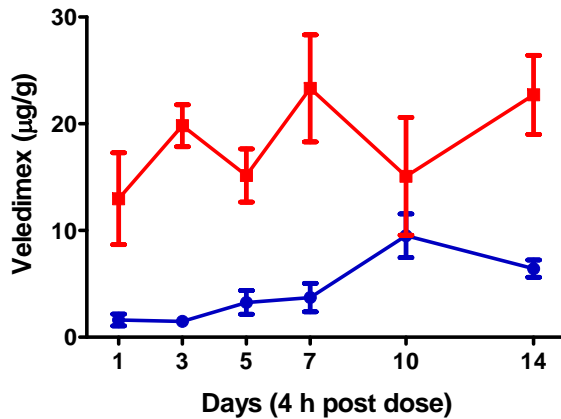
## Treatment Day 74



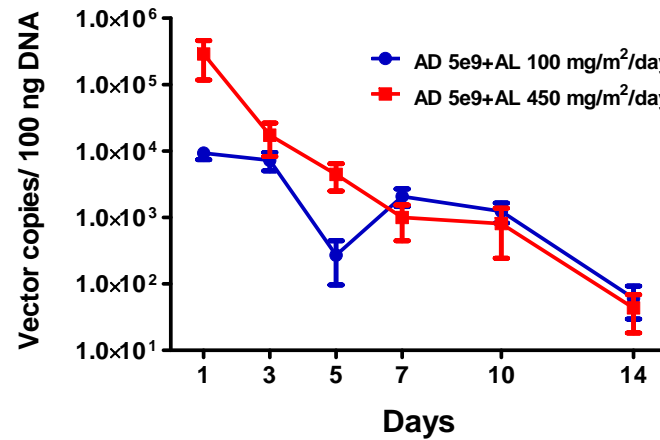
AL 450mg/m<sup>2</sup>/day BID x14  
+ Ad-RTS-mIL-12 1x10<sup>10</sup>vp

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

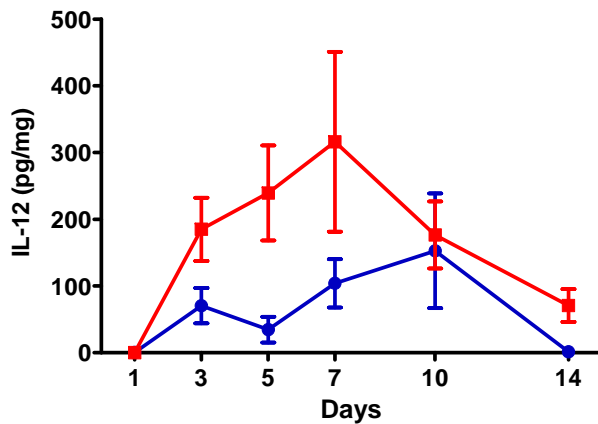
**Veledimex tumor**



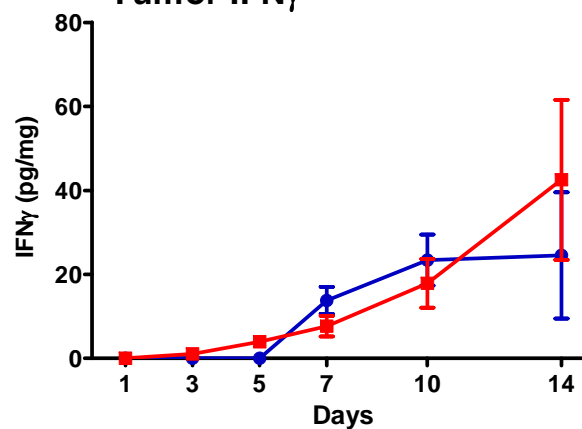
**Ad-RTS-mIL-12 tumor**



**Tumor IL-12**

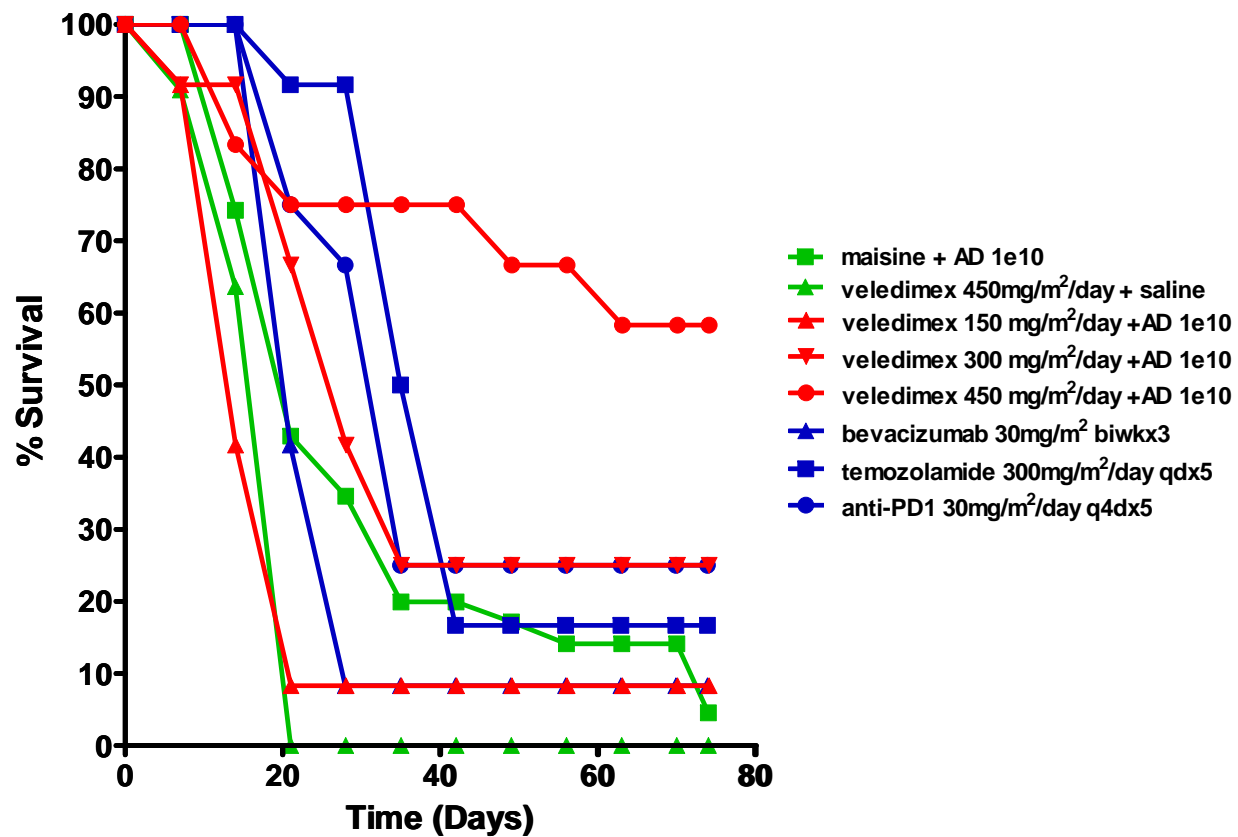


**Tumor IFN<sub>γ</sub>**

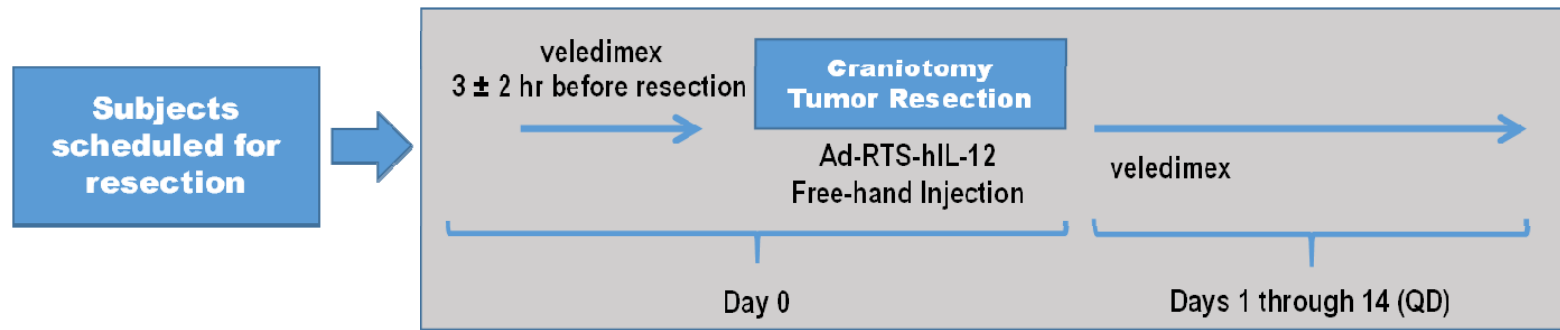


- Dose-related increase in tumor veledimex
- Tumor IL-12 correlates with vector copy, veledimex & mRNA IL-12
- Tumor IL-12 produced is biologically active
- Results indicate activation of innate immune system

# 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  $2 \times 10^{11}$  vp + veledimex 20mg (10mg/m<sup>2</sup>/day)

Most Common AEs

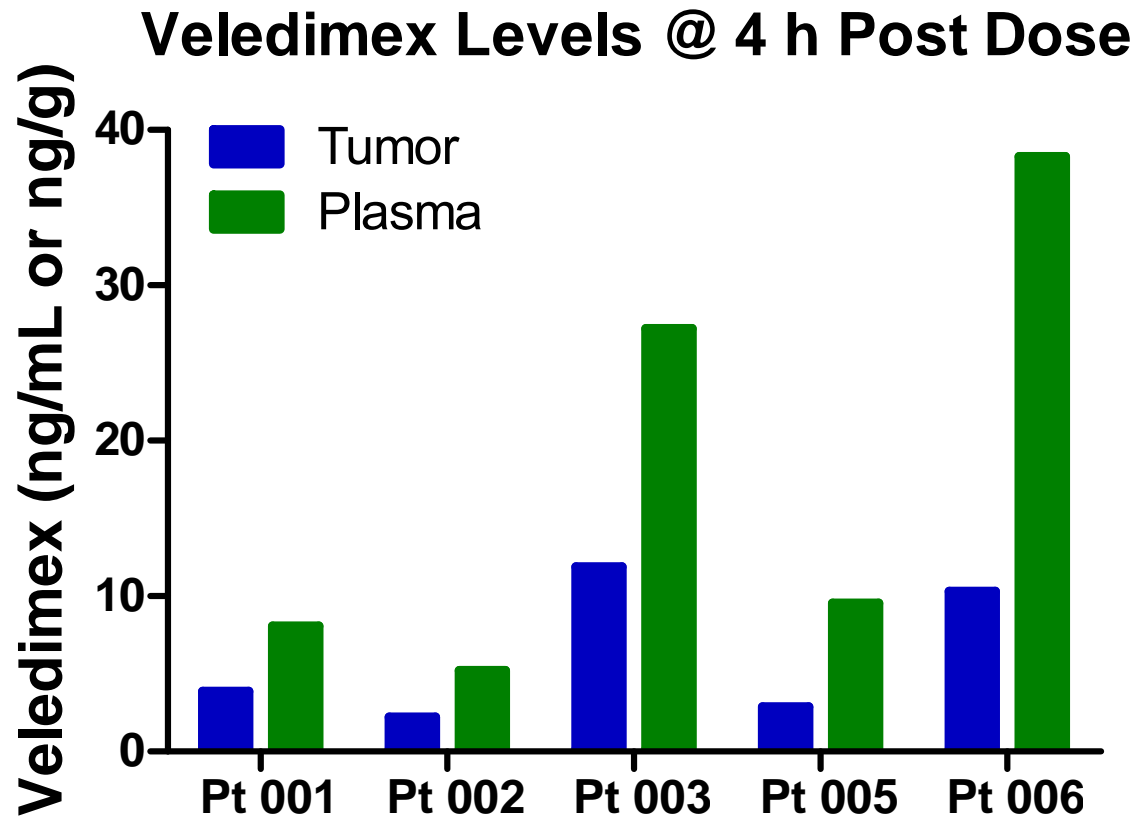
Headache, Fever, Hyponatremia, Nausea/Vomiting

Related SAEs

Aseptic Meningitis

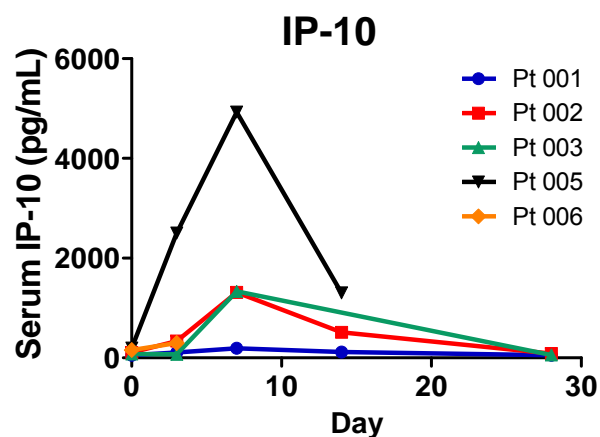
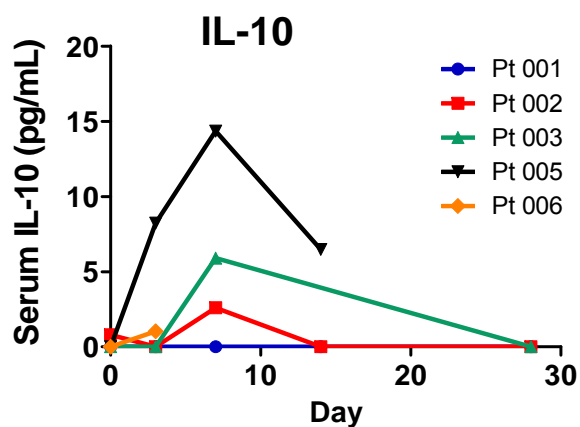
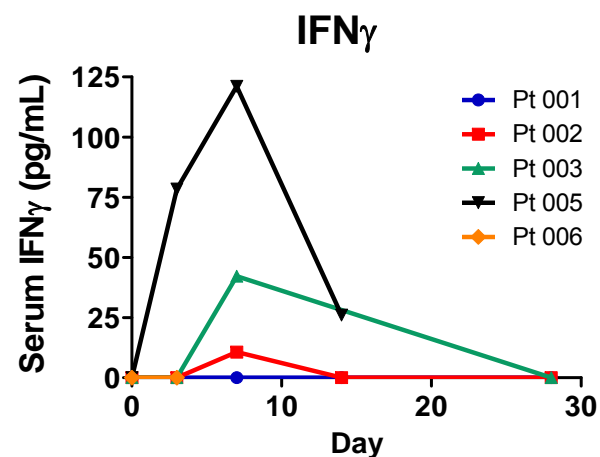
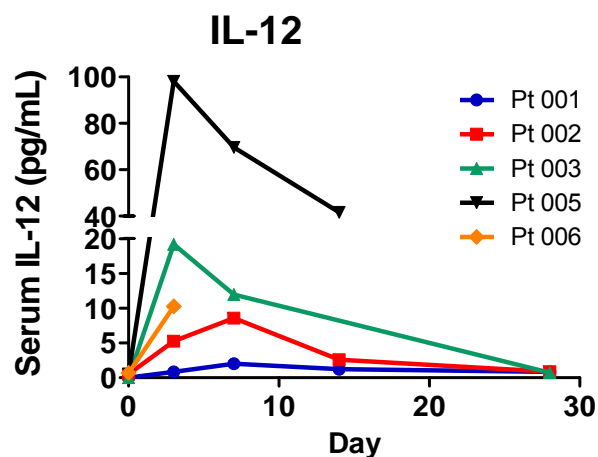
Neutropenia, Thrombocytopenia, Leukopenia

# Veledimex Crosses the Blood Brain Barrier



Veledimex 20 mg (10 mg/m<sup>2</sup>/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<sup>2</sup>/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  $\gamma$
- 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<sup>+</sup> 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 IFN $\gamma$  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<sup>®</sup> (RTS<sup>®</sup>) gene switch to extend the IL-12 therapeutic window