Retroviral Replicating Vector (RRV) Gene Therapy Platform
RRVs selectively infect cancer

- RRVs infect malignant tumors mainly due to known immune deficiency in cancer
- Yet RRVs are not normally human pathogens and have limited virulence genes to infect healthy cells

RRVs integrate in cancer cells
- Stealthily spread through tumor by budding rather than lysis

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Versatile RRV Platform Drives Pipeline

- **Near-Term**
  - Brain cancers

- **Mid-Term**
  - Other solid tumors

- ** Longer-Term**
  - Various product candidates
  - ADC targets
  - Immune activators
  - Suppress immune system brakes

- **Toca 511 (CD)**

*CD = cytosine deaminase*
Toca 511, our first RRV, Delivers Prodrug Activator Gene, CD

- 5-FC is selectively converted to 5-FU via CD within infected cancer cells
- 5-FU has a very short half-life, minimizing off-target effects
- 5-FU directly kills cancer cells and MDSCs within the tumor microenvironment
- In situ 5-FU production within infected cancer cells creates a high therapeutic index
Dual Mechanism of Action: Directly Cytolytic Plus Immune Activation

PAMPs = Pathogen Associated Molecular Patterns
DAMPs = Danger Associated Molecular Patterns
TLR = Toll Like Receptors
TAA = Tumor Associated Antigens
MDSCs = Myeloid Derived Suppressor Cells
Preclinical Studies of Toca 511 & 5-FC Demonstrate Activation of a Durable Immune Response Against Cancer

5-FU only action

5-FU plus immune actions

Human GBM in immune deficient mice

Syngeneic glioma in immune competent mouse model

Splenic immune cell activation assay

Reject re-challenge with same tumor in flank

No. of IFN-γ producing cells per 10,000 lymphocytes

Tumor size (mm²)

Days post challenge
Ascending Doses of Toca 511 and 5-FC Increase Survival

E3, E4, E5 = 10^3, 10^4, 10^5 TU/ gm brain
Tu-2449 glioma cells in B6C3 F1 mice
Toca 511 & Toca FC Selectively Turns Tumor into 5-FU Factory

Dual Actions: 5-FU Kills Tumor and Activates Immune System Against Cancer

Brain and tumor samples from Tocagen clinical trial patients

CD = cytosine deaminase
Preclinical efficacy is supported in many cancers

- brain cancer
- colorectal cancer
- pancreatic cancer
- breast cancer
- prostate cancer
- lung cancer
- bladder cancer
- ovarian cancer