Ultrasound-enhanced delivery and improved efficacy of an oncolytic Vaccinia virus in a murine bladder cancer model

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OxSonics THERAPEUTICS

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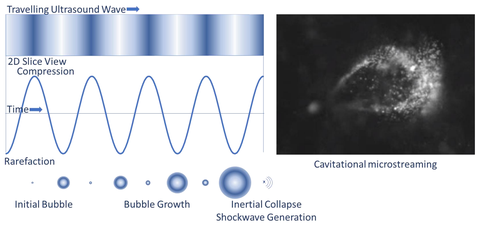
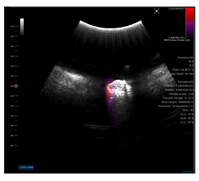
AIM AND HYPOTHESIS

- Oncolytic viruses hold potential as cancer treatment but poor pharmacokinetics and tumor penetration hamper their clinical application.
- A novel, non-invasive approach to tackle this problem is SonoTran. This technology enhances drug delivery thanks to ultrasound- induced inertial cavitation from sub-micron bubbles co-infused with the drug.

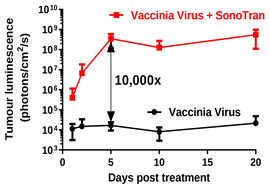


- In this two-part project, the ability of SonoTran (ST) platform to enhance delivery and efficacy of an unarmed oncolytic Vaccinia virus (VV) encoding the luciferase gene (SKV-Luc) was investigated.

SONOTRAN BACKGROUND



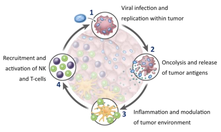
Cavitation signal (in color scale) quantified by PAM and overlaid on B-mode imaging



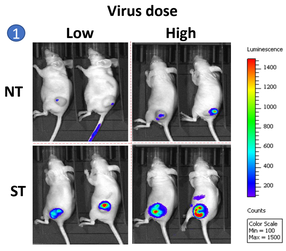
SonoTran enhanced delivery of Vaccinia virus [Myers et al, Mol. Therapy (2016)]

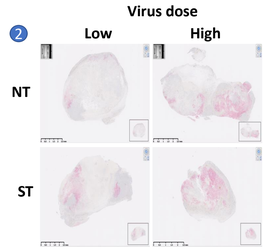
ENHANCED VACCINIA VIRUS BACKGROUND

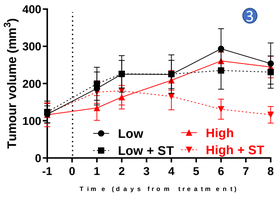
Turnstone's proprietary vaccinia virus platform has been engineered to stimulate the immune system, drive antigen presentation and recognition, and re-shape the tumor microenvironment (www.turnstone.com).

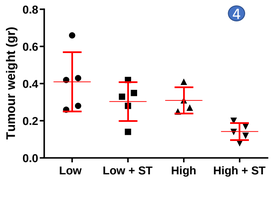


DELIVERY AND SHORT TERM EFFICACY RESULTS



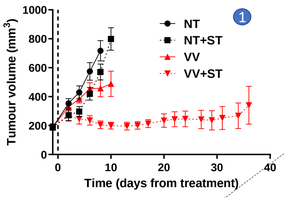


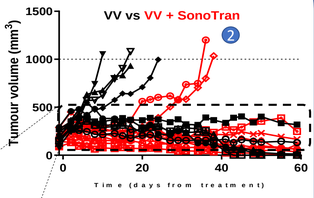


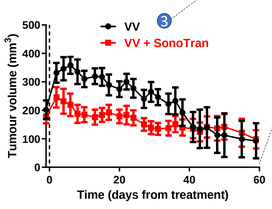


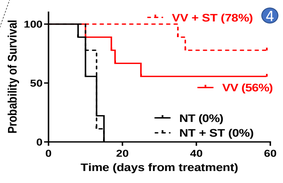
1. **Improved virus delivery (*in vivo* imaging at day 2)**
2. **Increased virus staining (IHC of VV *ex vivo* at day 8)**
3. **Decreased tumor volume**
4. **Decreased tumor weight at culling**

LONG TERM EFFICACY RESULTS









1. **Decreased tumor volume**
2. **Increased time to tumor progression in partial responders (17.5 ± 6 vs 36 ± 1 days)**
3. **Decreased tumor volume in strong responders**
4. **Increased overall mice survival (78% vs 56%)**

CONCLUSION

- **Addition of SonoTran to systemically administered, unarmed Vaccinia virus treatment enhanced the virus delivery in tumor, improved the efficacy of the treatment and increased the survival of treated mice.**
- **Overall, SonoTran treatment resulted in smaller average tumor sizes and higher numbers of responders to the treatment.**

METHODS

- Mice implanted with UM-UC-3 human bladder cancer cells were divided into 4 cohorts when tumors reached an average size of 150-200 mm^3:

1. Delivery and short term efficacy study (8 days)

a-b) Low virus dose +/- SonoTran, n=5
c-d) High virus dose +/- SonoTran, n-5

2. Long term efficacy study (until tumor volume = 1000mm^3)

a) Untreated control (NT), n=9
b) SonoTran only (ST), n=9
c-d) High virus dose (VV) +/- SonoTran, n=9

- Cavitation nuclei and virus were administered intravenously just before ultrasound application from the OxSonics SonoTran system.

Ultrasound parameters: fc=0.5MHz; 8000cycles; PRF=0.5Hz; PRFP=1.59-2.03MPa variable.

- Ultrasound amplitude was set according to the cavitation monitoring method (passive acoustic mapping [PAM]) to be within 0.1–0.5 nJ/pulse for 5 minutes of treatment.

The author has conflict of interest with the following corporate organization: OxSonics Therapeutics

TURNSTONE BIOLOGICS

Takeda