cullinan AMBER

A Cullinan Oncology Company

Mining for Tomorrow's Cures

Intratumoral administration and retention of IL-2 and IL-12 bifunctional fusion proteins to drive a systemic immune response

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December 14, 2021

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Amber First Principles

1. Cytokines are autocrine/paracrine in nature, ***not endocrine***
   - ➡ Cytokines should be administered locally rather than systemically

2. A protein injected locally will not stay local without ***retention***
   - ➡ A retention domain is key to enhancing local bioavailability

3. Natural responses consist of a ***cytokine milieu***, not individual cytokines
   - ➡ Synergistic cytokines should be co-delivered

Intratumoral Delivery of Drug Does Not Guarantee Retention in Tumor

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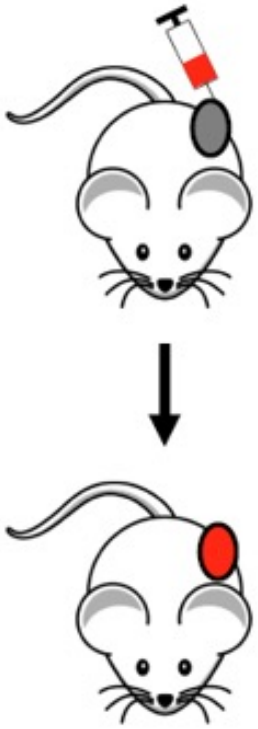
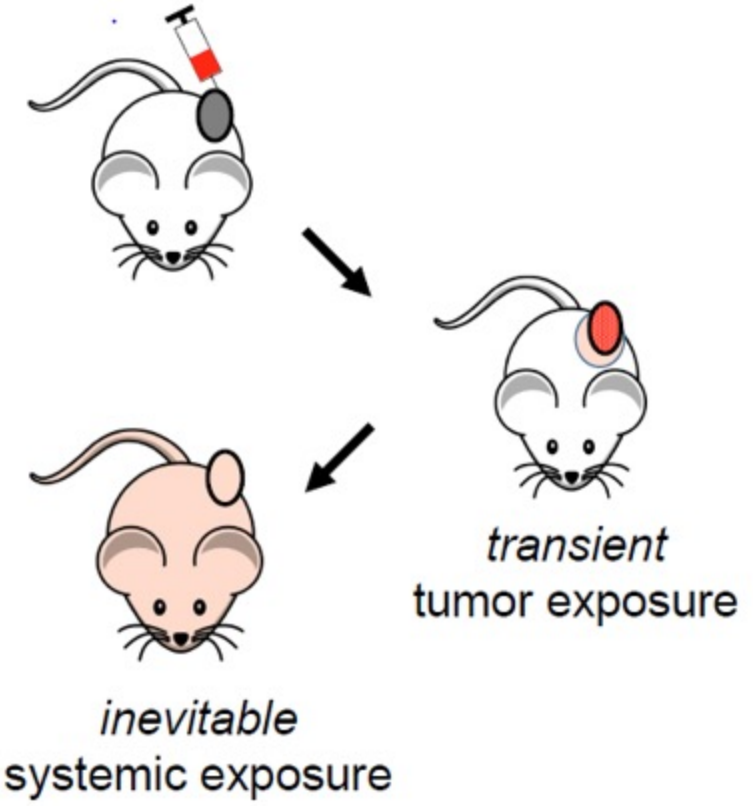
Intratumoral Drug Delivery

Expectation



Reality



Rohner & Thomas JCR 2016

IL-2 + IL-12 Is A Highly Synergistic Cytokine Combination

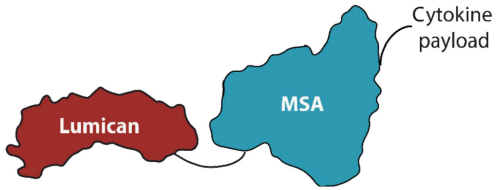
- IL-2 and IL-12 combine to potently induce orthogonal JAK and STAT signaling pathways
- IL-2 upregulates the IL-12 receptor, thereby poising effector cells for enhanced Th1 signaling
- The two cytokines synergize to enhance production of anti-tumoral cytokines (e.g., IFNγ, TNFα), proliferation of effector cells, and anti-tumoral killing activity
- IL-2 and IL-12 have shown synergistic activity in a variety of preclinical tumor models, whether administered through gene therapy, oncolytic viruses or recombinant protein injection

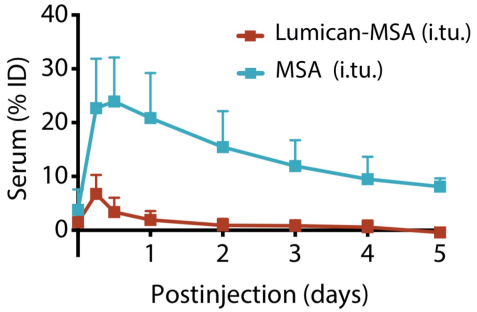
However, systemic toxicities have limited opportunities to explore combination of the two potent antitumor cytokines

Gollob, JA, et al. *J Immunol*, 1999; Hanagiri, T, et al. *Cancer Immunol Immunother*, 1996; Addison, C, et al. *Gene Therapy*, 1998.; Wigginton, JM, et al. *JCI*, 2001; Gillies, SD, et al. *Cancer Immunol Immunother*, 2002; Momin, N, et al. *STM*, 2019; Liao, et al. *Nature Immunology*, 2011.

IT Injection of Collagen-Anchored Cytokine Fusions Are Retained, Improving Therapeutic Index

- The Cullinan Amber platform is based on technology from the Wittrup lab at MIT
- Lumican, a collagen binding protein, and mouse serum albumin, a bulky spacer domain, were fused to cytokines to promote retention following IT delivery



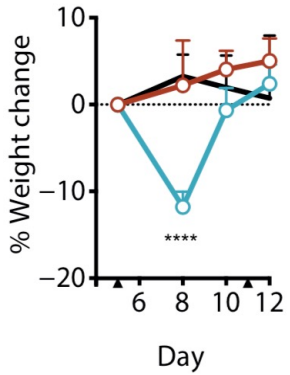


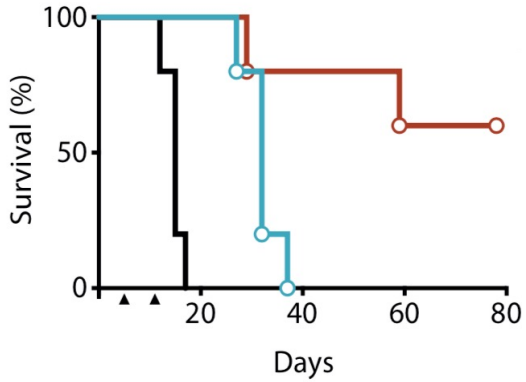

Dane Wittrup

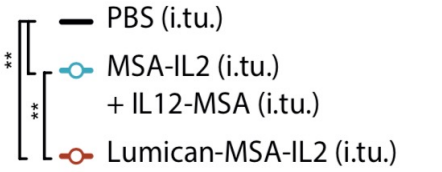

Noor Momin

- Locally retained cytokine fusions had improved safety and efficacy relative to unretained fusions

B16F10 Tumors:





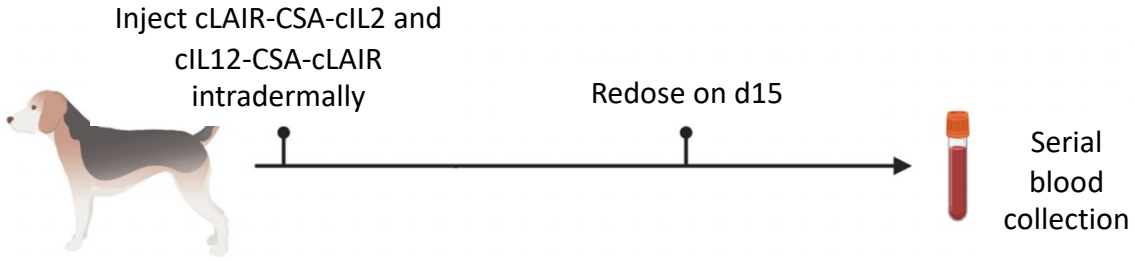


The goal of Cullinan Amber is to generate multifunctional constructs with robust single-agent antitumor activity

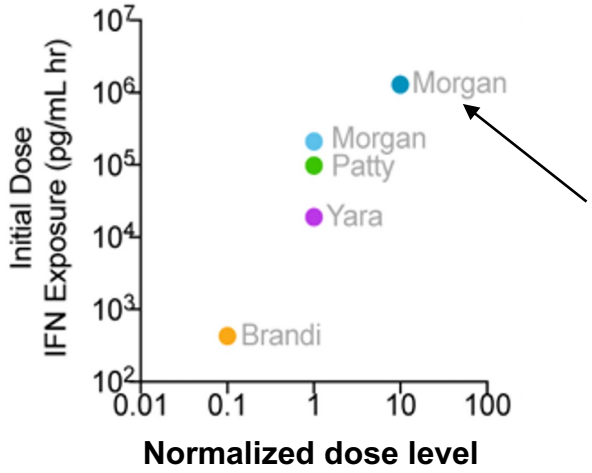
Momin, et al. *Science Translational Medicine*, 2019.

Proof of Concept in Dogs: Local Administration of Retained Cytokines - Safety

- Canine surrogates of LAIR-MSA-2 and 12-MSA-LAIR were tested in healthy beagles
- Cytokines injected intradermally; likely overestimates toxicity due to more systemic leakage than IT



- Systemic IFNγ Levels correlated with dose and toxicity



- Only dog at highest dose level exhibited transient CRS symptoms
- Dose was 10x higher than standard cytokine MTD

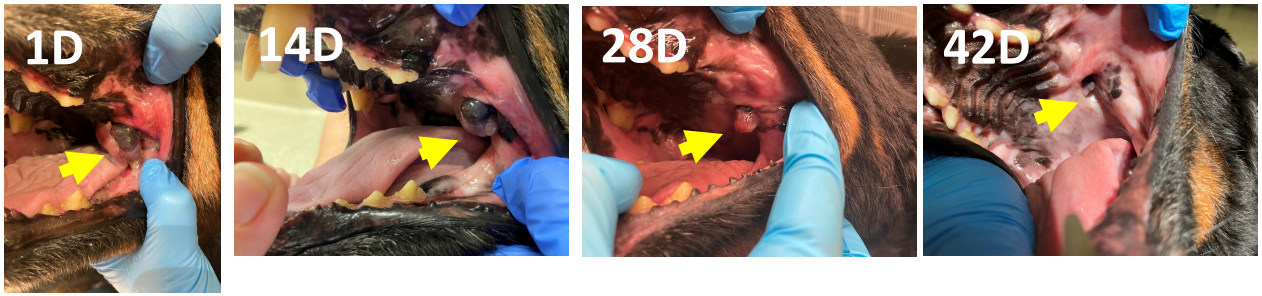
➢ **Study demonstrated the safety and tolerability of collagen-anchored cytokines in larger mammals**

K. Dane Wittrup (MIT) and Timothy M. Fan (Illinois, Urbana-Champaign)

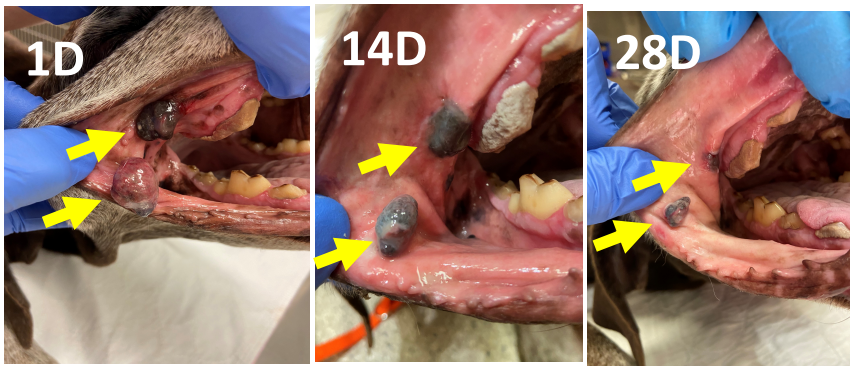
Proof of Concept in Dogs: Local Administration of Retained Cytokines - Efficacy

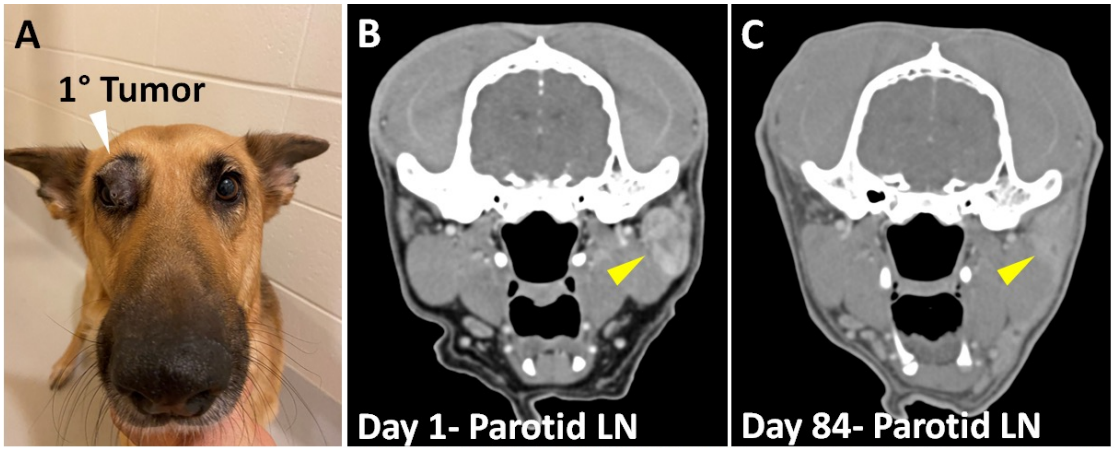
- Ongoing dose escalation studies in dogs with malignant melanoma and soft tissue sarcoma
- First cohort complete (n=3 per cohort); enrolling second cohort at double the dose

Examples from first cohort:



Example from second cohort:



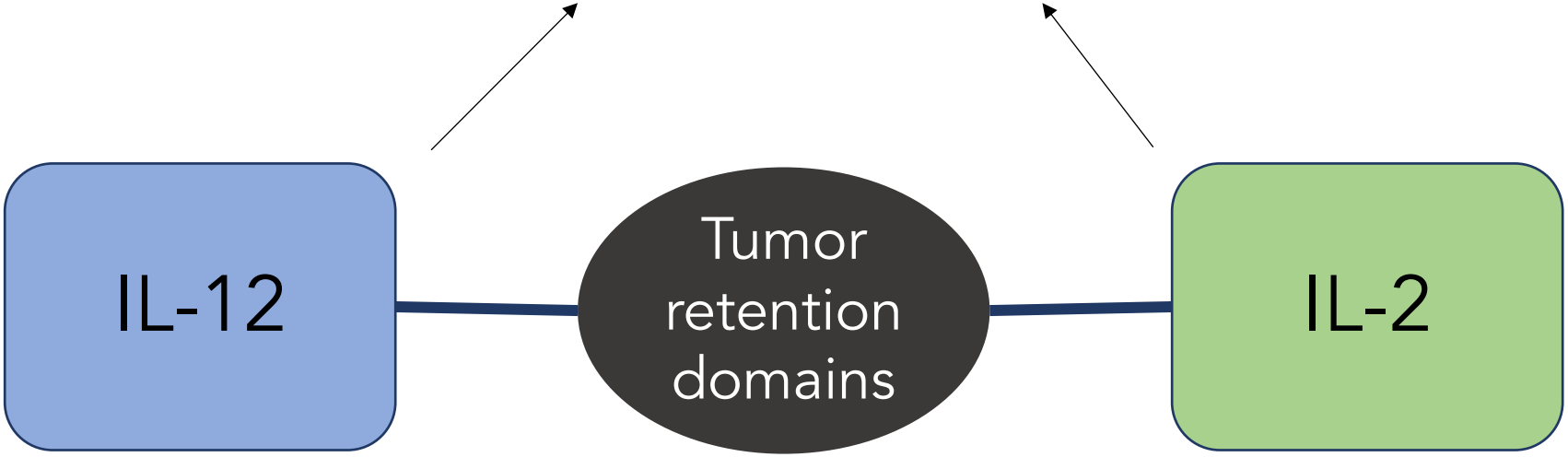


- In some dogs, ulceration and inflammation may be indicative of pseudo-progression
- Local vaccine-like effect may be sufficient to drive regional immunosurveillance

K. Dane Wittrup (MIT) and Timothy M. Fan (Illinois, Urbana-Champaign)

The Cullinan Amber Approach: Intratumoral Delivery of Dual Cytokine Fusion

IL-12 and IL-2 act synergistically in promoting Th1 anti-tumor immunity



Two mechanisms of retention:

- By collagen binding
- By bulky overall size

Amber is single-chain polypeptide to aid in manufacturing

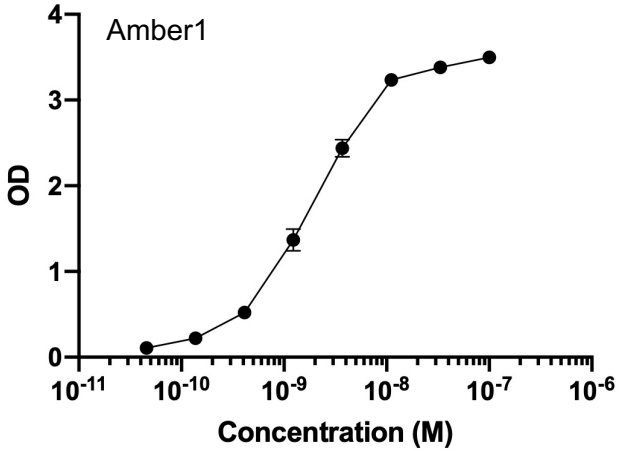
Cullinan Amber is a First-In-Class Cytokine Delivery Product

1. Only Amber co-delivers IL-2 and IL-12 as a single agent
2. No other cytokine fusion proteins are being developed for IT delivery to maximize safety/efficacy
3. Retention domains are encoded into the polypeptide chain without the need for additional biomaterials

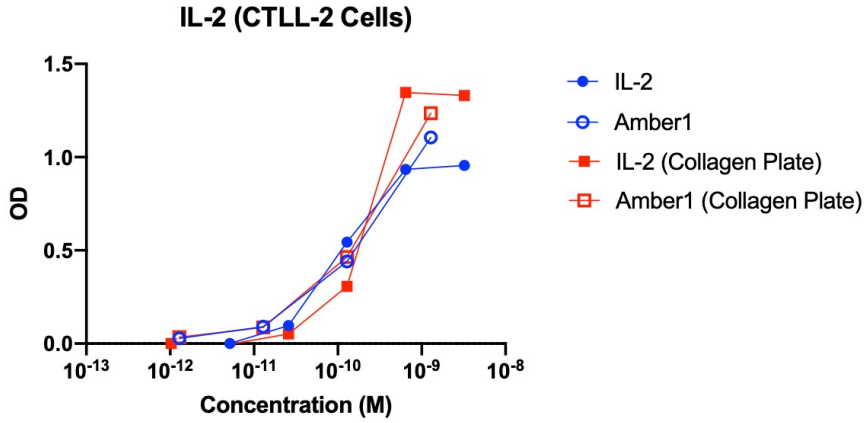
Functionality of Cytokines in Amber

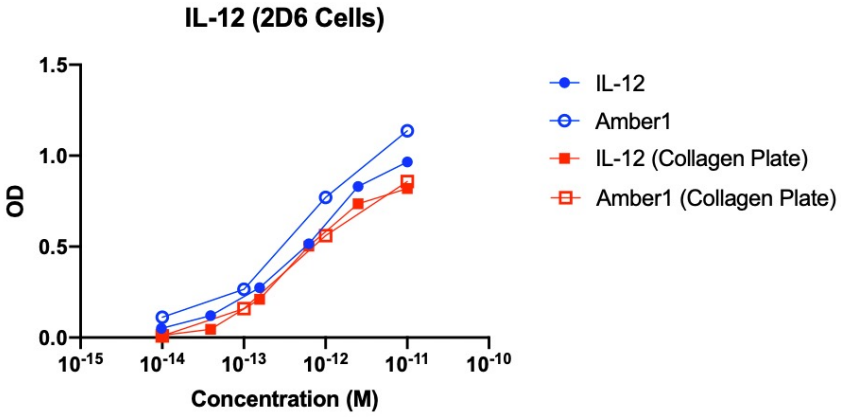
Amber binds to collagen with nM affinity

Murine surrogates used throughout presentation



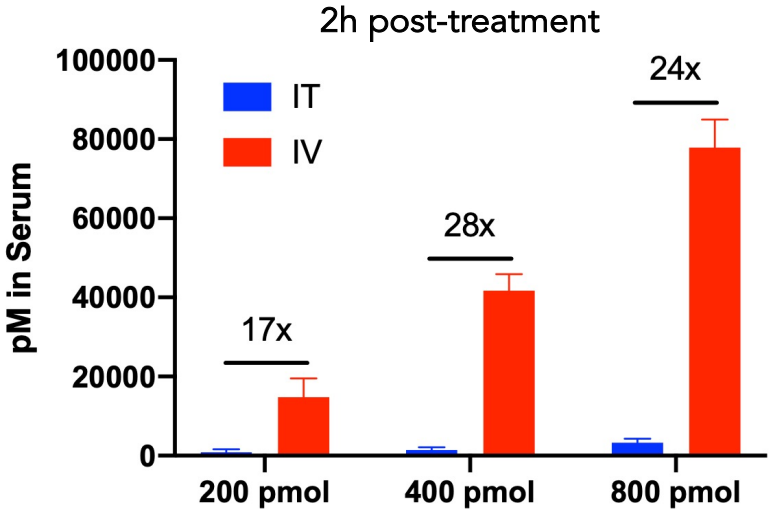
Both IL-2 and IL-12 remain functional in Amber, even when pre-bound to collagen-coated plates



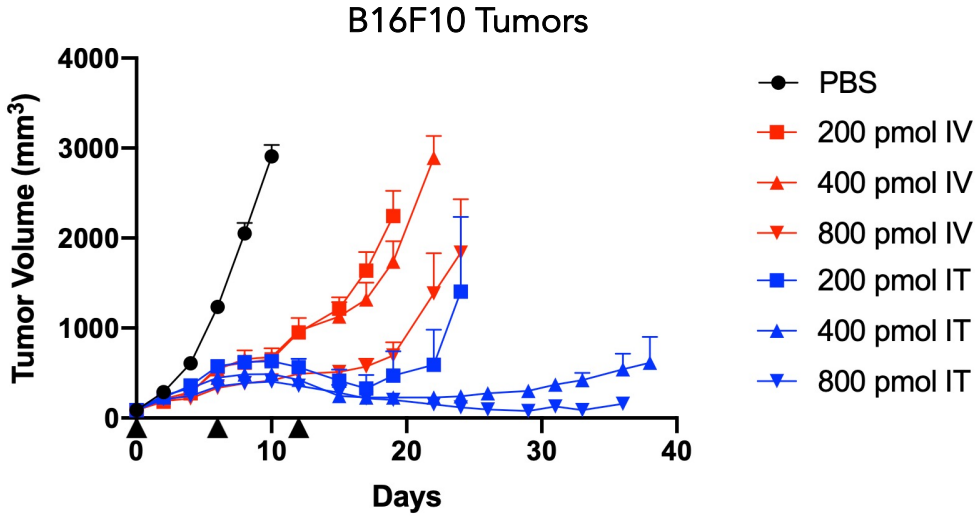


IT Administration Reduces Systemic Exposure and Enhances Anti-Tumor Response

Levels of Amber following IT vs IV treatment



Efficacy advantage of IT delivery



Retention of IT-Administered Cytokines Is Key to Reducing Toxicity

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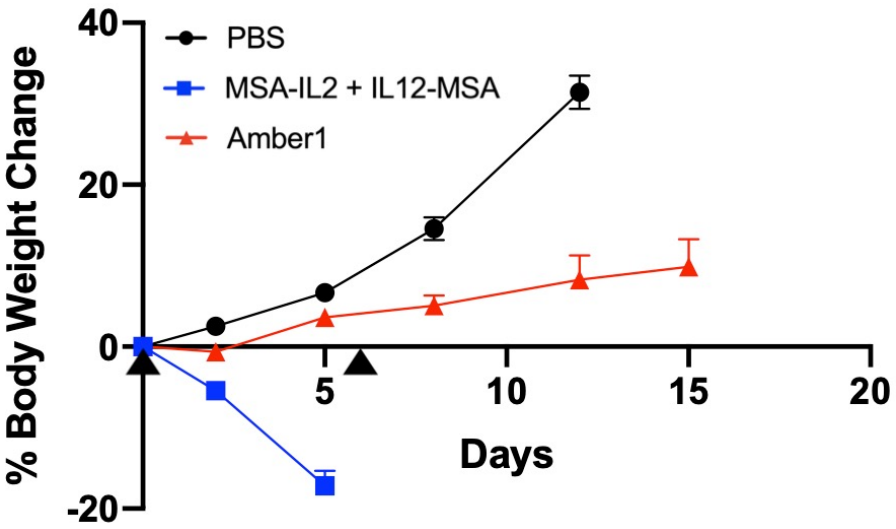
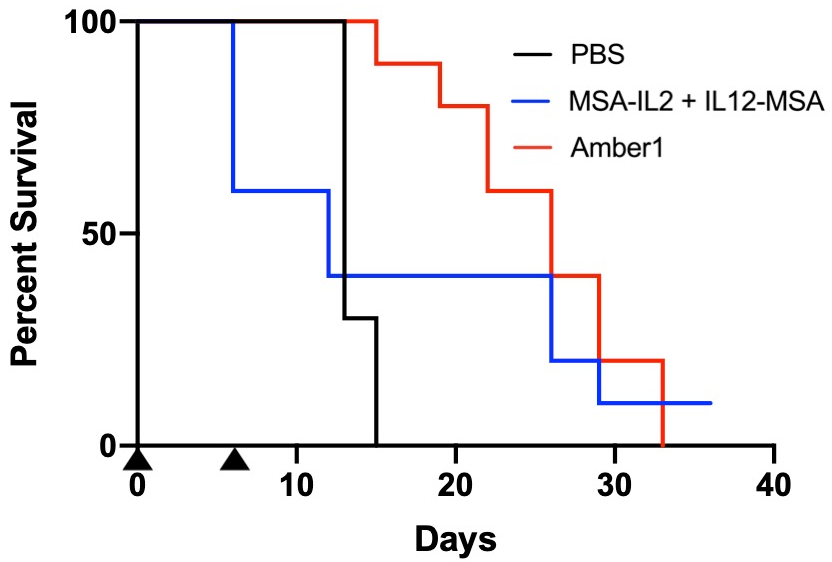
IT treatment with and without retention domain

B16F10 Tumors





Robust Control of Checkpoint-Refractory Tumors in Mice

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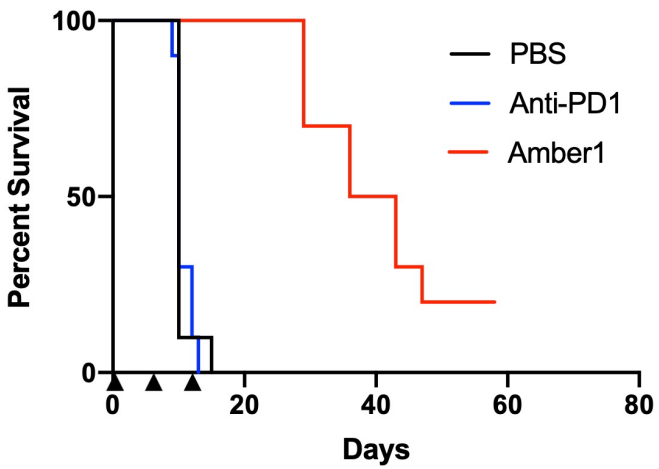
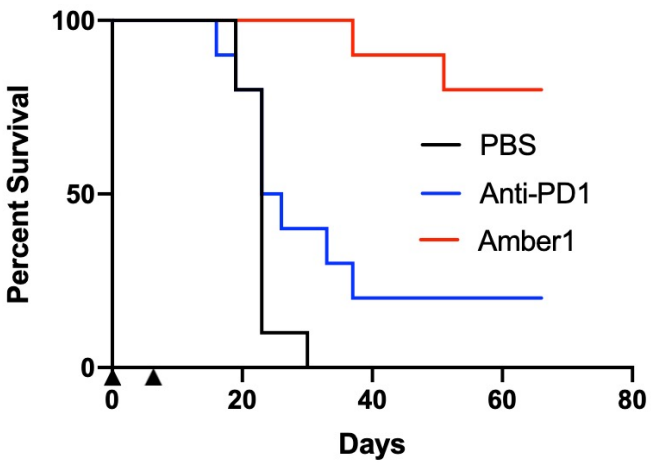
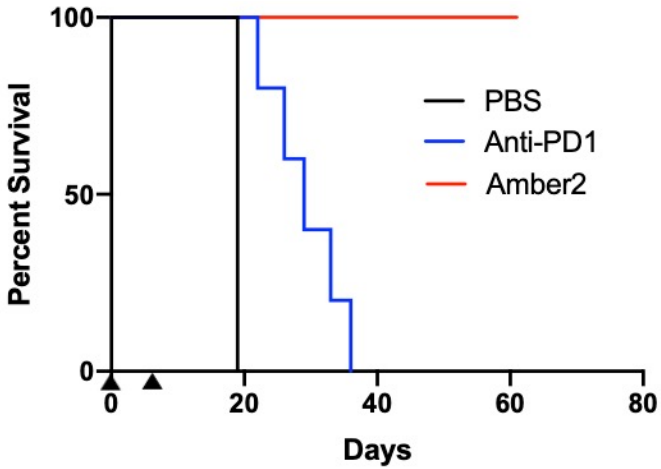
B16F10



CT26



MC38



Systemic and Memory Responses as Monotherapy or in Combination with Anti-PD1 in MC38 Model

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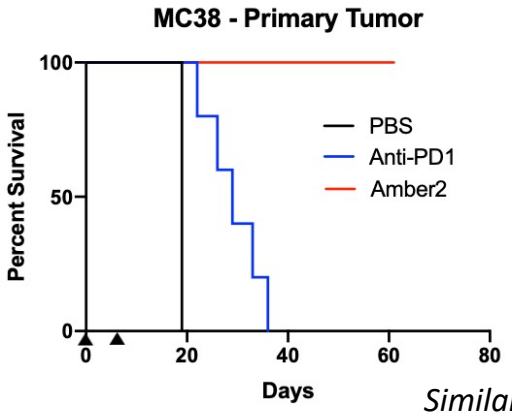
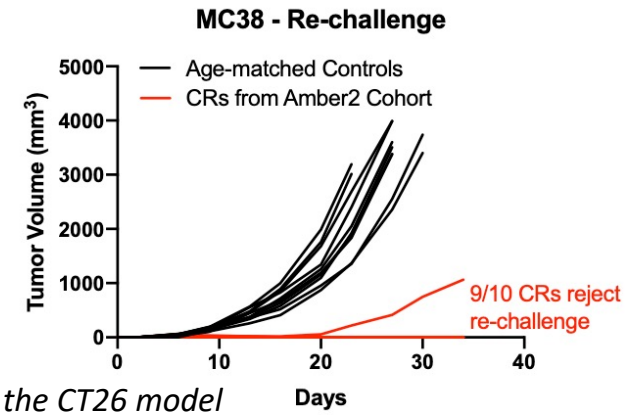
Primary Tumor Results



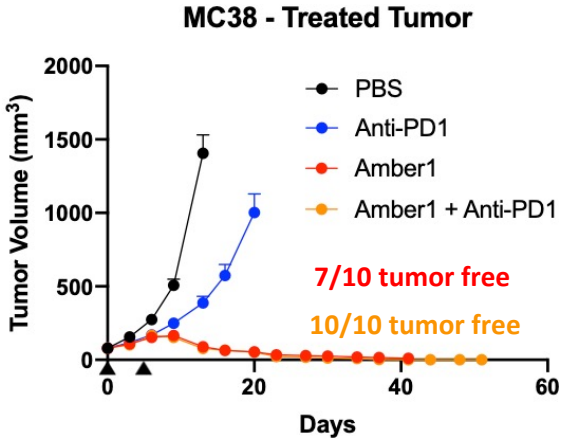
Rechallenge Amber CR's

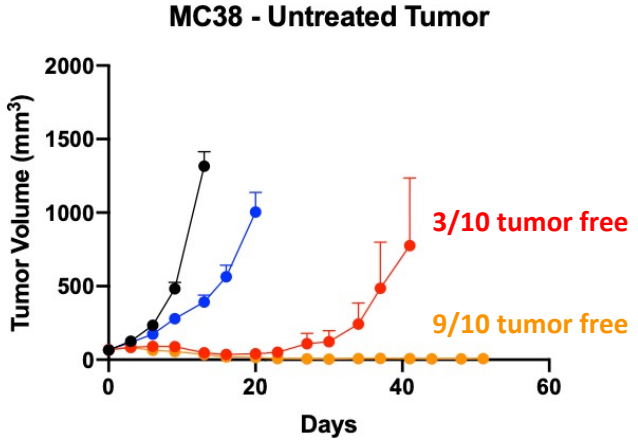
Re-challenge Study



Similar data observed in the CT26 model

Treatment of Dual Flank Tumors: Monotherapy + Combination with Anti-PD1 CPI

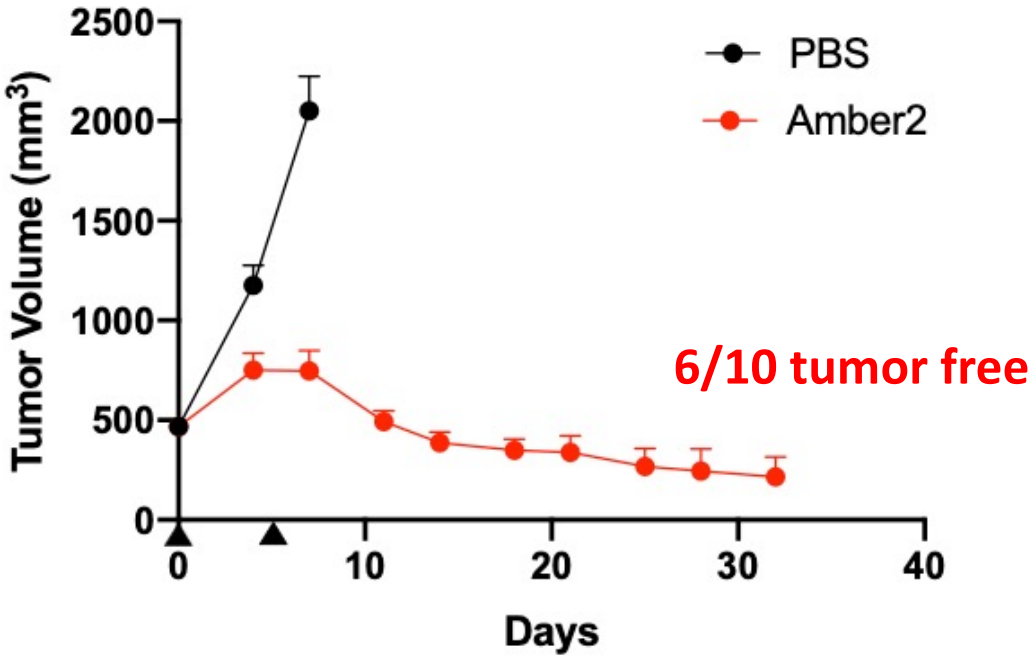




Synergy with anti-PD1 checkpoint inhibitor

Responses With Treatment of Large Established Tumors in the MC38 Model

Large Established Tumors (500 mm^3)



Cullinan Amber is a first-in-class bifunctional agent that locally co-delivers IL-2 and IL-12 in a safe and effective manner

1. Cytokines are autocrine/paracrine in nature, ***not endocrine***
   - ➡ Amber is administered locally
2. A protein injected locally will not stay local without ***retention***
   - ➡ Amber is retained via bulky size and collagen binding
3. Natural responses consist of a ***cytokine milieu***, not individual cytokines
   - ➡ Amber delivers both IL-2 and IL-12 in a safe and effective manner

- Preclinical data suggests that single-agent activity is expected in the clinic across multiple tumor types
- An IND filing is anticipated in 2022

Acknowledgments

Cullinan Amber Team

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