

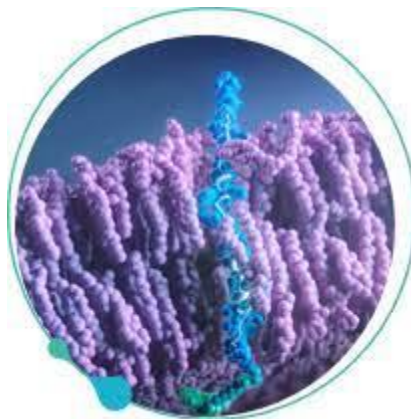
MOLECULAR TARGETS AND CANCER THERAPEUTICS

October 7-10, 2021

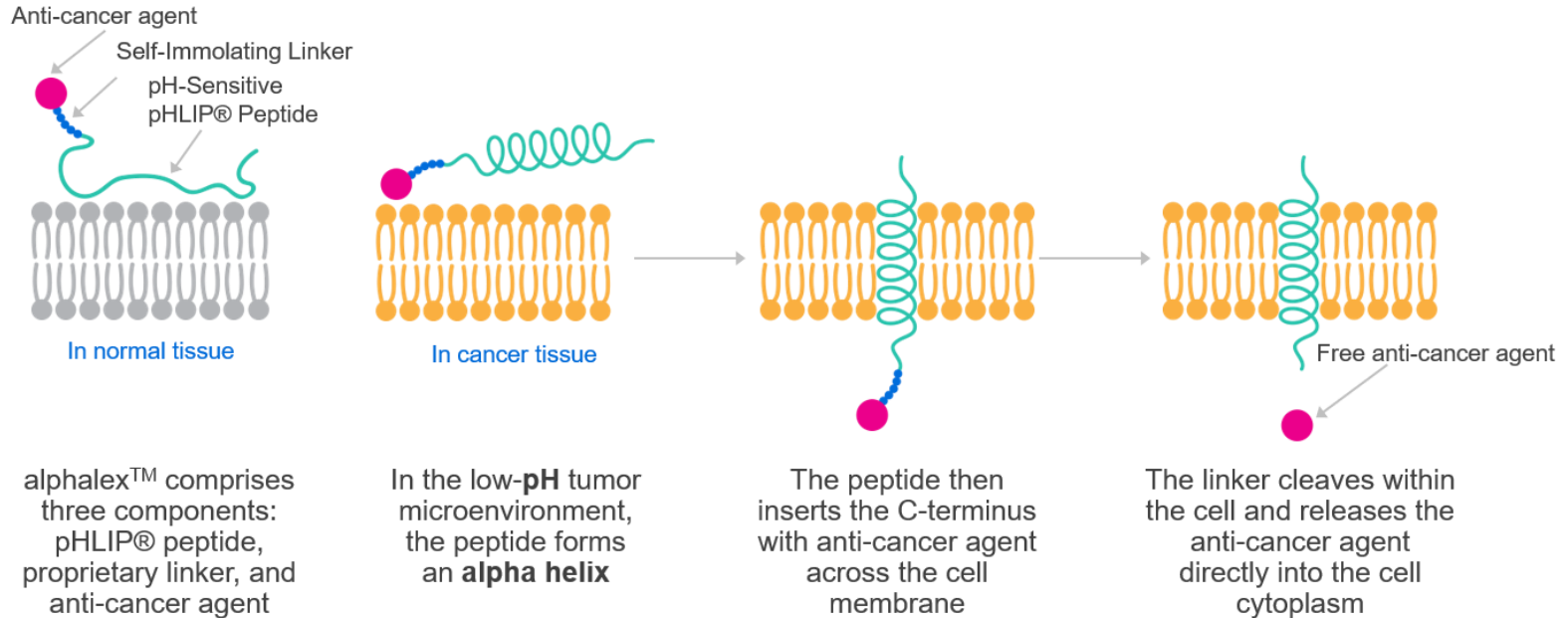
CBX-12 (alphalex™-exatecan) sensitizes tumors to immune checkpoint blockade in an antigen agnostic manner by immune activation

Presenter: Sophia Gayle

Cybrex Therapeutics, New Haven CT



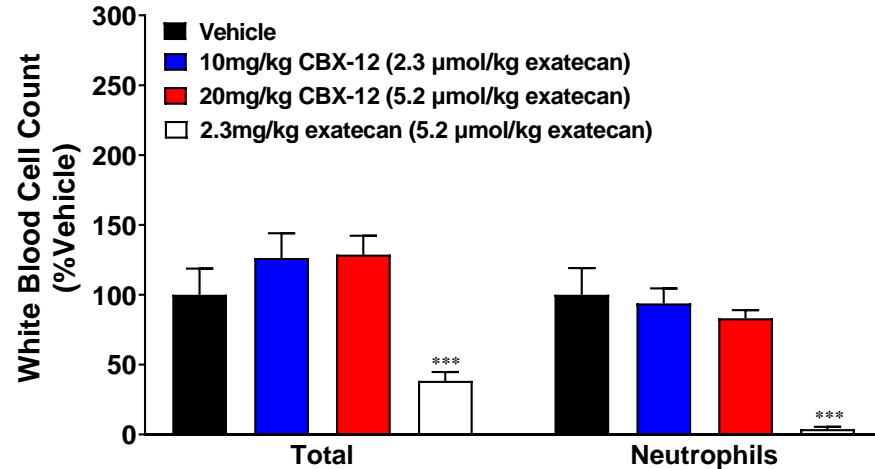
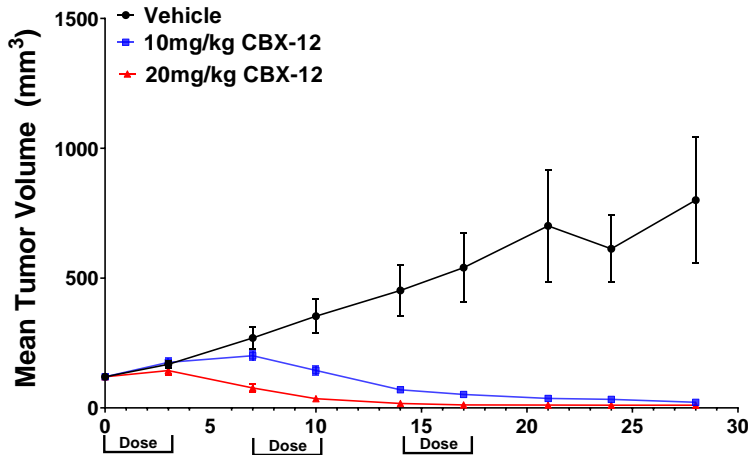
How We Do It: alphalex™ Selectively Targets Tumor Cells



Platform has been validated by a number of institutions and investigators in academia and industry, with an extensive body of published preclinical data

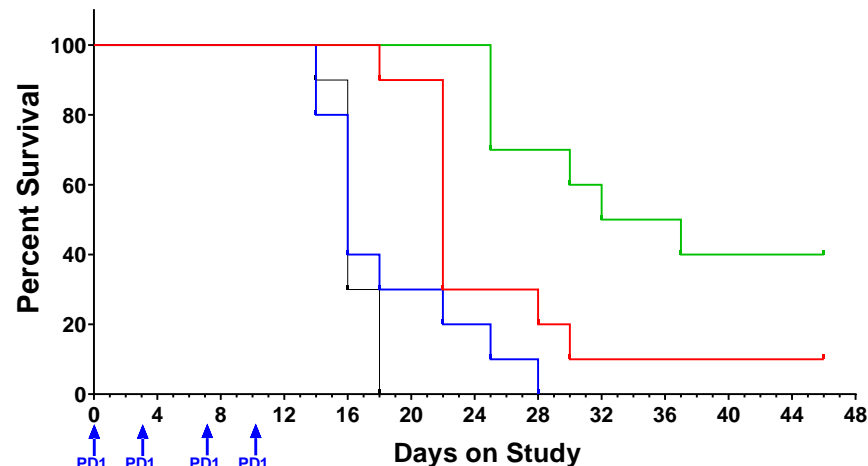
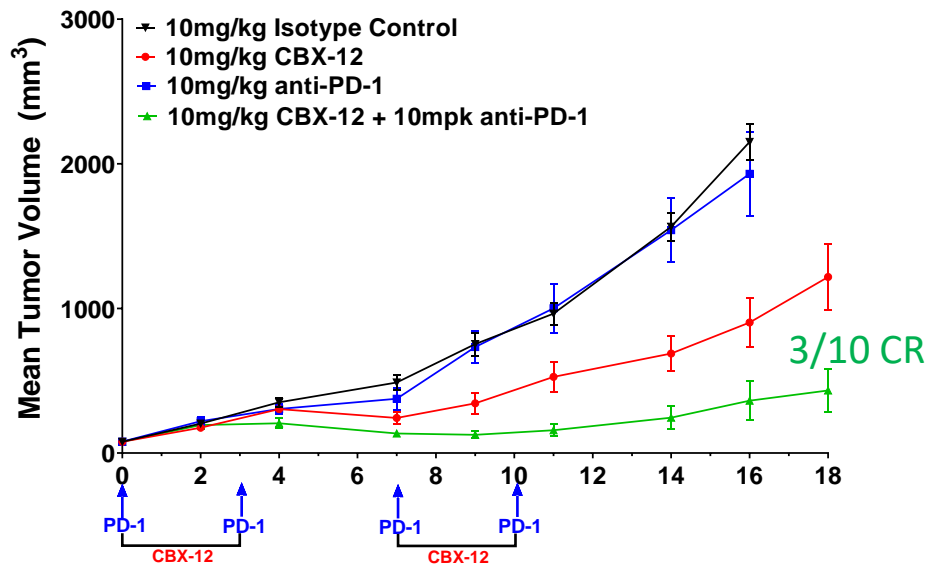
CBX-12: Selective Delivery of Exatecan to Tumors with Avoidance of Normal Tissue Tox

**Avoidance of leukocytopenia and immunosuppression
Greater potential for combinations with immunomodulatory drugs**



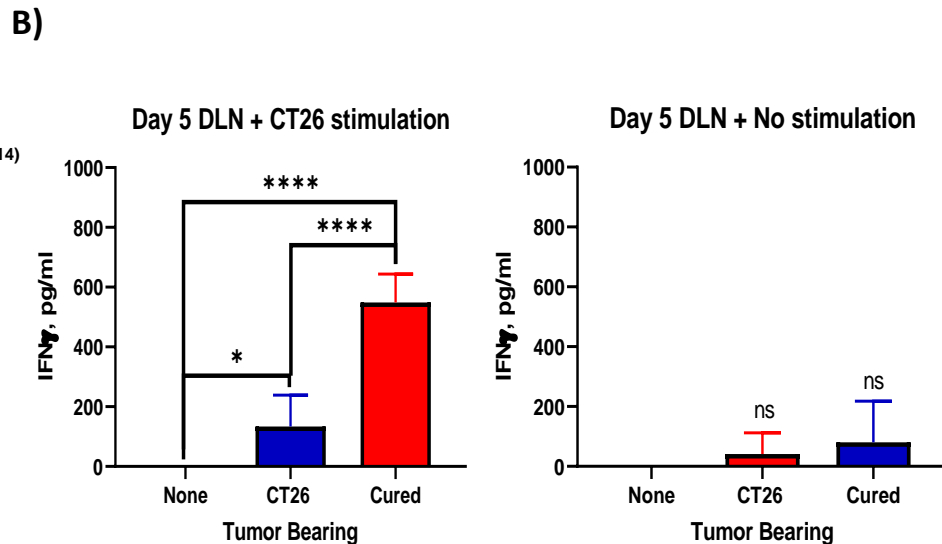
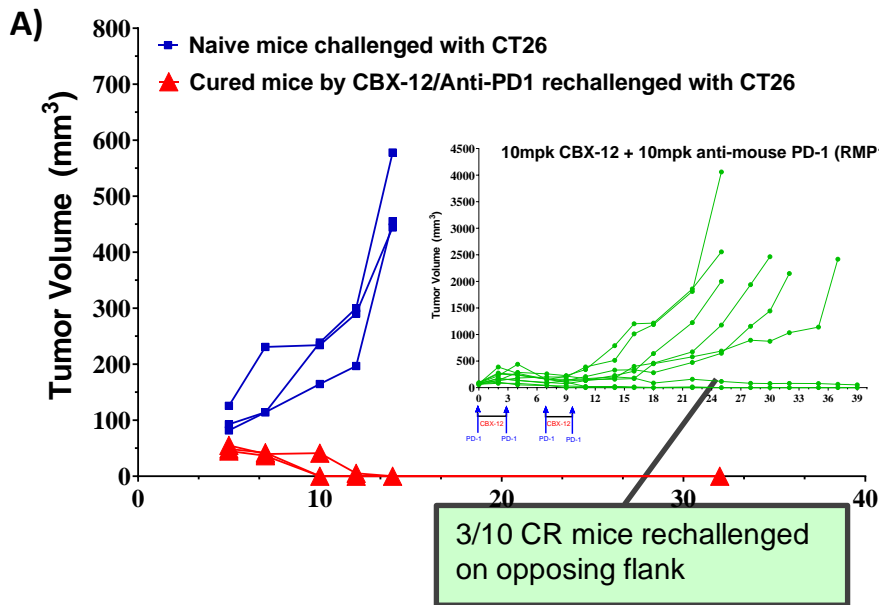
- Left: Activity of CBX-12 in GA2157 gastric PDX model after dosing 10 or 20 mg/kg QDx4/wk x 3 weeks. Study is ongoing.
- Right: Profile of white blood cell counts after 4 days of dosing the indicated dose of CBX-12 or an equimolar dose of unconjugated exatecan in nude mice

CBX-12 Synergizes with anti-PD1 in CT26 Colorectal Syngeneic Model



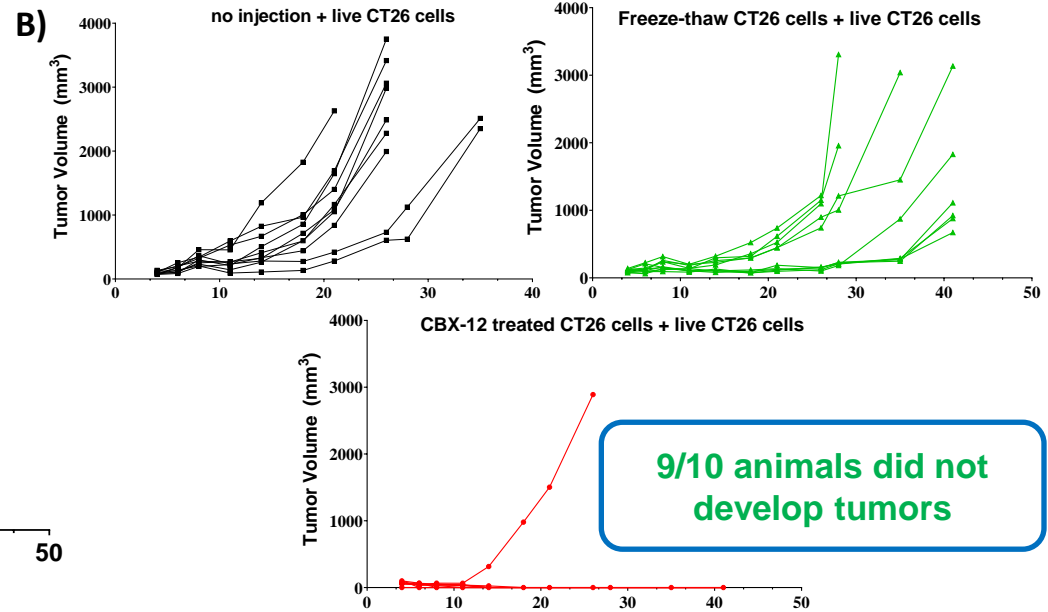
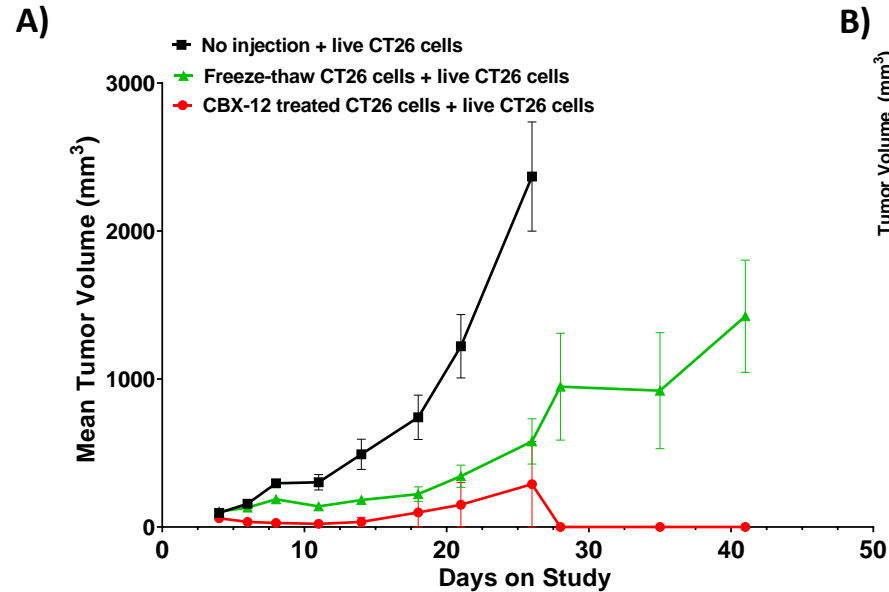
- Left: Activity of CBX-12 combination with anti-PD-1 in CT26 colorectal model after dosing 10 mg/kg CBX-12 QDx4/wk x 2 weeks and anti-PD1 Q4D x 4 as single agent and in combination.
- Right: Kaplan Meier survival analysis of combination study. The combination resulted in a significant survival benefit, with three animals undergoing a complete response.

CBX-12/anti-PD1 Combo Generates Long Term Anti-Tumor Immunity



- A.** The 3 CR mice from the CBX-12/PD1 combination arm (inset) were rechallenged with CT26 cells on the opposing flank (red). An additional 3 naive mice were injected with CT26 cells as a control (blue).
- B.** 55 days after the rechallenge, draining lymph nodes from the 3 CR mice were isolated and single cell suspension incubated with inactivated CT26 cells in vitro. Draining lymph nodes from mice bearing CT26 tumors and no tumor were used as controls. IFN γ production was measured after 5 days incubation.

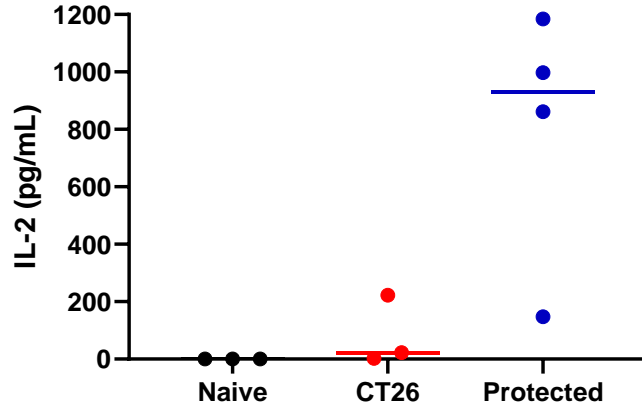
CBX-12 Induces Immunogenic Cell Death to Confer Long Term Immunological Memory



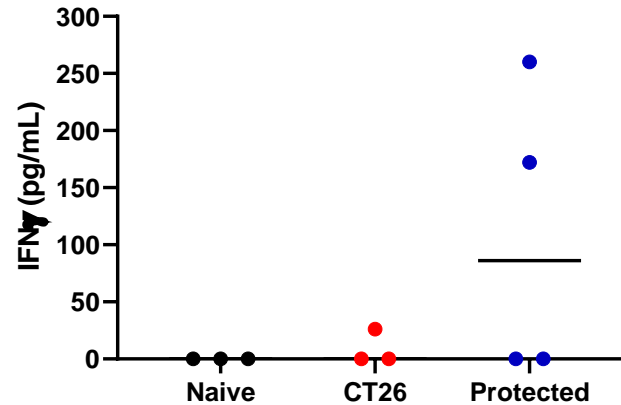
- A.** Balb/c mice were vaccinated by cells killed *in vitro* by either freeze thawing or by CBX-12 treatment. Two weeks later, animals were injected on the same flank with a booster of freeze thawed or CBX-12 treated cells. 7 days post-vaccination, mice were re injected with live CT26 cells on the opposing flank.
- B.** Spider plots of the study represented in (A). 9/10 mice in the CBX-12 arm remained tumor-free throughout the course of the experiment, while all animals in the control groups developed tumors.

Cytokine Biomarkers of Immunological Memory in CBX-12-Vaccinated Mice

A) IL-2 Production by Splenocytes



B) IFN γ Production by Splenocytes



Ex vivo stimulation of splenocytes of CBX-12 vaccinated mice with CT26 cells results in production of IL-2 and IFN γ

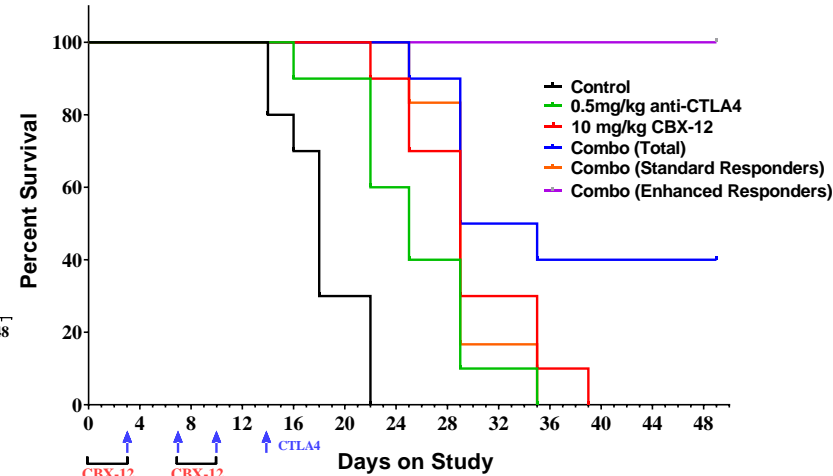
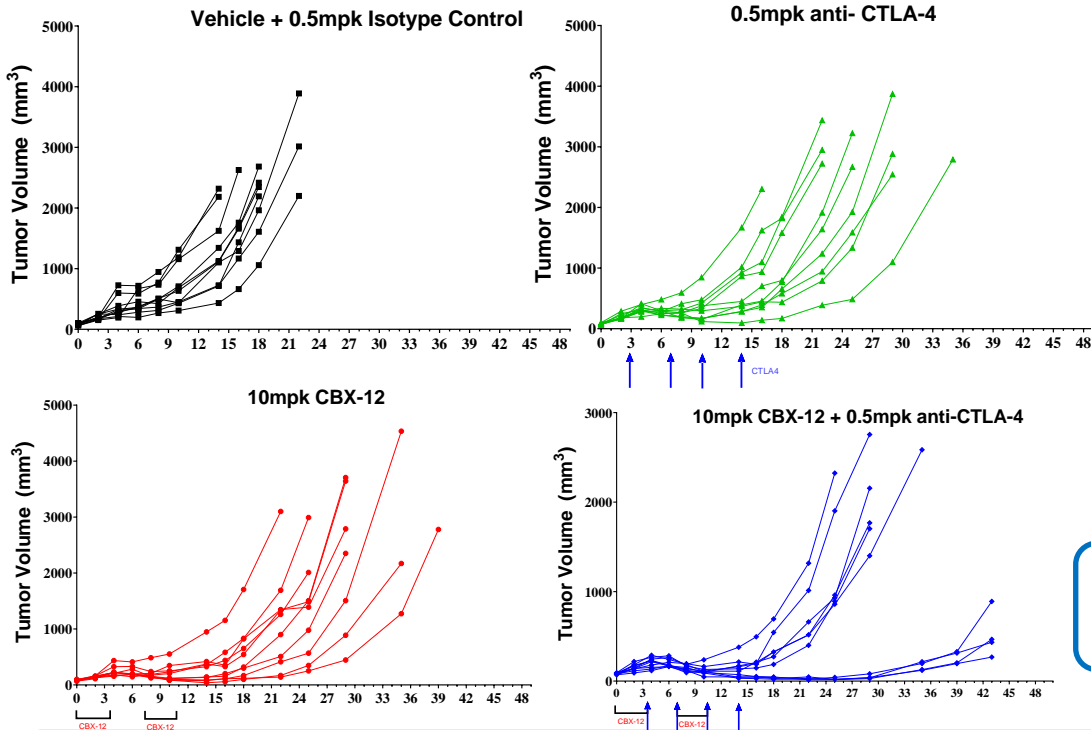
Naive: no vaccination + no CT26 challenge

CT26: no vaccination + CT26 challenge-tumor bearing

Protected: vaccination + CT26 rejection

- A. Induction of IL-2 in supernatant of splenocytes cultured ex vivo from naïve, CT26 tumor bearing, and CBX-12 vaccinated animals after 6 days of co-culture with inactivated CT26 cells.
- B. Induction of IFN γ in supernatant of splenocytes cultured ex vivo from naïve, CT26 tumor bearing, and CBX-12 vaccinated animals after 5 days of co-culture with inactivated CT26 cells.

CBX-12 Synergizes with anti-CTLA4 in CT26 Colorectal Syngeneic Model



4/10 combination animals demonstrate prolonged tumor regression >24 days

- Left: Spider plots of CBX-12 combination with anti-CTLA4 in CT26 colorectal model after dosing 10 mg/kg CBX-12 QDx4/wk x 2 weeks and 0.5 mg/kg anti-CTLA4 Q4D x 4 as single agent and in combination.
- Right: Kaplan Meier survival analysis of combination study.

- CBX-12 treatment results in tumor selective delivery of efficacious levels of exatecan while avoiding toxicity to normal tissues including immune components
- CBX-12 synergizes with anti-PD1 and anti-CTLA4
 - Responders display long term anti-tumor immunological memory in part due to the induction of immunogenic cell death by CBX-12
- Cybrexa aims to test immunotherapy combinations with CBX-12 clinically in 2022