Evaluating drug delivery methods and αPD-1 combination therapies in a murine colorectal cancer model

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Introduction
- Colorectal cancer (CRC) is the third most diagnosed cancer and the third leading cause of cancer-related deaths in men and women in the US.
- CRC can be treated with immunotherapy, specifically with immunotherapy, specifically with immunotherapy.
- Cold tumors consist of few immune cells, making it less likely to respond to an IC
d.

Hypothesis
- Delivery of celecoxib via oral administration will have comparable effectiveness as IP injections.

Methods
- COX-2 is an overexpressed enzyme in the tumor microenvironment.
- Higher levels of COX-2 expression are correlated with shorter survival times and larger tumors in cancer patients.
- Celecoxib, a COX-2 inhibitor, can block COX-2.
- Increasing celecoxib doses in CRC mouse models can improve tumor growth.
- A limitation to studying celecoxib in CRC mouse models is that it is injected twice daily, leading to:
  - Pain and discomfort
  - Additional stress
- Pain and stress can have physiological or biological impacts, resulting in experimental bias and difficulty interpreting data in animal models.

Goals
- To evaluate an alternative delivery method of celecoxib to avoid repeated injections.
- This experiment compares two methods of delivering celecoxib:
  1. Intraperitoneal (IP) injections
  2. Oral delivery via chow

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Does celecoxib improve the efficacy of CKM + αPD-1?

Celecoxib delivery methods do not have a significant impact on tumor incidence, progression, growth rate or survival.

Future Questions
- Does celecoxib improve the efficacy of CKM + αPD-1?
- Explore additional treatments: control, CKM, αPD-1, celecoxib, CKM + αPD-1, celecoxib.
- Is the immune response affected?
- How is the immune response affected?

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References


Figure 1. T cell regulation via the immune checkpoint pathway programmed death-1 (PD-1). A shows the activation of the pathway versus the inhibition by IP αPD-1 antibody shown in B.

Figure 2. A method for turning "cold" tumors "hot".
- Cold tumors consist of few immune cells, making it less likely to respond to an IC.
- Hot tumors consist of many immune cells, making it more likely to respond to an IC.
- CKM can turn cold tumors into hot tumors by regulating intratumoral chemokine expression to favor recruitment of immune cells.

Figure 3. Experimental design. On day 0, twenty C57BL/6 mice were subcutaneously injected with 5 × 10⁶ MC38 cells to induce CRC tumors. All 20 mice received CKM on days 4 and 6 via IP injection and all 20 mice received 0.2 mg/kg celecoxib via IP injection.

Figure 4. While mice receiving celecoxib via IP injection and chow both gained weight following tumor inoculation, celecoxib-fed mice gained more weight. N = 10/group; p values determined by 2-way ANOVA.

Figure 5. Tumor incidence and regression are similar regardless of delivery method.
- A. 50% of the injected group and 50% of the chow group never exhibited a palpable tumor. N = 10/group; p values determined by log rank test.
- B. Among mice with palpable tumors, 2/3 (43%) and 3/5 (60%) experienced tumor regressions with injected and chow celecoxib, respectively. N=10/group.

Figure 6. Mice administered celecoxib via IP injection demonstrated a trend towards faster tumor growth compared to those with ad libitum celecoxib chow. When comparing early-stage tumors (within 3 weeks of inoculation), the injected group had slightly larger tumors than the chow group. N = 10/group; p values determined by 2-way ANOVA.

Figure 7. Overall survival is similar regardless of delivery method. Two of the mice in the chow group have died as compared to 4 mice in the injected group. N=10/group; p values determined by log rank test.