Laboratory of Targeted Drug Delivery and Nanomedicine

Liposomal Resiquimod for Treatment of Colorectal Cancer Metastasis

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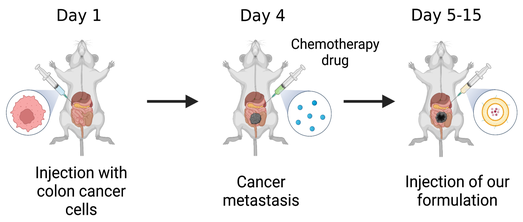
Introduction

Peritoneal metastasis of colorectal cancer is currently treated by cytoreductive surgery and hyperthermic intraperitonal chemotherapy. However, despite the aggressive approach there are high recurrence rates. We have developed two liposomal formulations that delivers a toll-like receptor agonist Resiquimod (R848) to promote immune cell activation in the peritoneal cavity. One monovalent formulation contains 1,2-stearoyl-3-trimethylammonium-propane chloride (DSTAP), a cationic lipid. The other contains a cell penetrating peptide (CPP) and is a multivalent lipid formulation. Survival of mice undergoing combination treatments with liposomes, R848 and oxaliplatin at different dosages were investigated in this study. To determine whether the issue with relapse persisted with this treatment, treated mice were rechallenged with the original and new tumor cell lines. Both CPP-R848 and DSTAP-R848 treated mice showed full CT26 rejection with some showing rejection of the new tumor. All Free R848 treated mice developed the new tumor and one re-developed CT26.

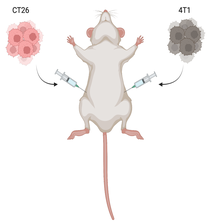
Methods

Survival study:



Dosages tested: 2, 1, 0.5 mg/kg
Study length: 120 days.
Mice were monitored and weighed daily after treatment.

Rechallenge study:



Mice were subcutaneously inoculated with CT26 and 4T1 cells on their right and left flanks to determine if mice developed immune memory as recurrence is common.

Tumour measurements were taken every other day and study length was 25 days.

Results

Survival study:

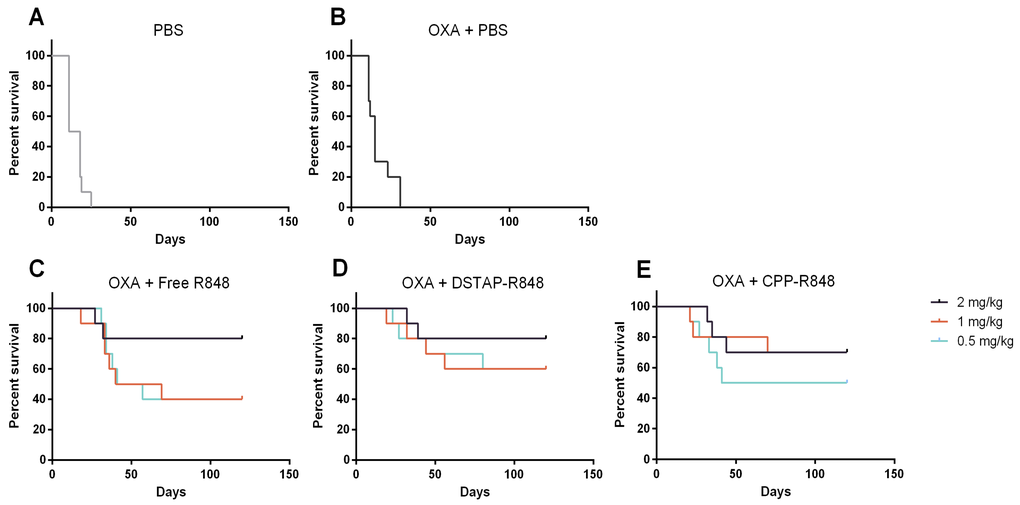


Figure 1. 120-day survival across differerent treatments and their dosages. Mice are treated with the following treatments: (A) PBS only, (B) Oxaliplatin + PBS, (C) Oxaliplatin + Free R848, (D) Oxaliplatin + DSTAP-R848, (E) Oxaliplatin + CPP-R848

Rechallenge study:

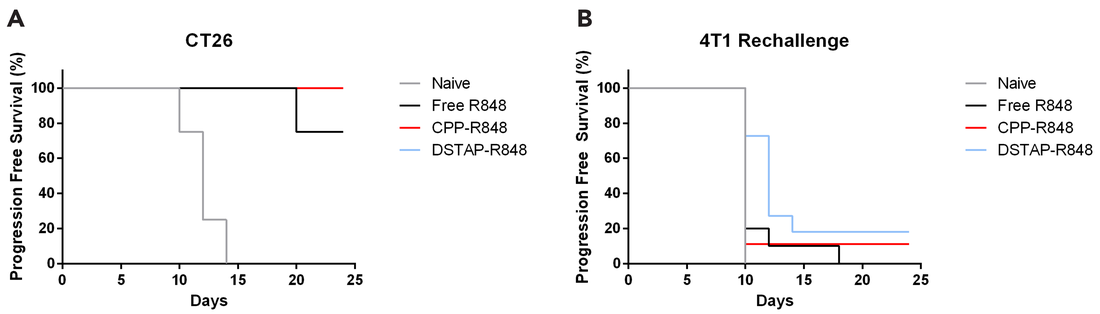
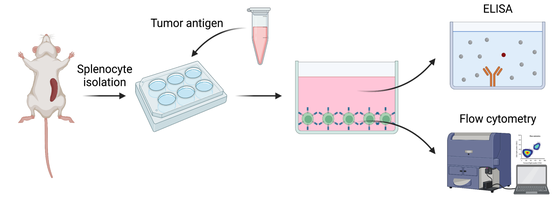


Figure 2. Progression free survival from a 24 day rechallenge study with 4T1 and CT26 cells on cured and naive. (A) Cured mice vs. naive mice rechallenged with CT26 cells (B) Cured mice vs. Naive mice rechallenged with 4T1 cells. (n=4 for naive, n=11 for Free drug, n=13 for DSTAP and n=12 for CPP.

Future Studies

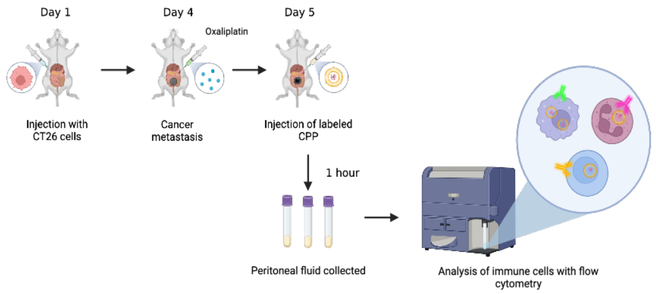
Splenocyte study:



Purpose: To validate the immune memory effect generated by treatment with CPP+R848, DSTAP+R848 or Free R848.

Hypothesis: When exposed to CT26 tumor antigen we will see increased IgG production and clonal expansion of B-cells. We expect the highest level of IgG to be from either CPP or DSTAP and lower levels will be seen in the Free drug group.

Immune uptake study:



Purpose: To identify which immune cell populations take up the CPP formulation the most.

Hypothesis: While the DSTAP formulation is heavily taken up by dendritic cells, we expect there will be higher macrophage involvement in the CPP formulation thus resulting in a different mechanism of uptake.

Conclusion

Based on the dosage studies, a minimum of 1 mg/kg of CPP-R848 achieves 70% efficacy, 2 mg/kg of DSTAP-R848 can achieve 80% efficacy and 2 mg/kg Free R848 can achieve 80% efficacy but not all mice treated with Free R848 developed immune memory against the original tumor.
Mice treated with DSTAP and CPP formulations had better controlled 4T1 tumor growth compared to Free drug. 2 mice from the DSTAP-R848 group rejecting the new tumor while 1 mouse from the CPP-R848 group rejected the new tumor.

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