A MULTIDRUG FORMULATION OF PEGYLATED LIPOSOMES WITH CO-ENCAPSULATED ALENDRONATE, DOXORUBICIN AND MITOMYCIN-C LIPID-BASED PRODRUG FOR CHEMOIMMUNOTHERAPY OF CANCER

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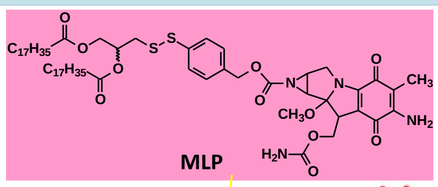
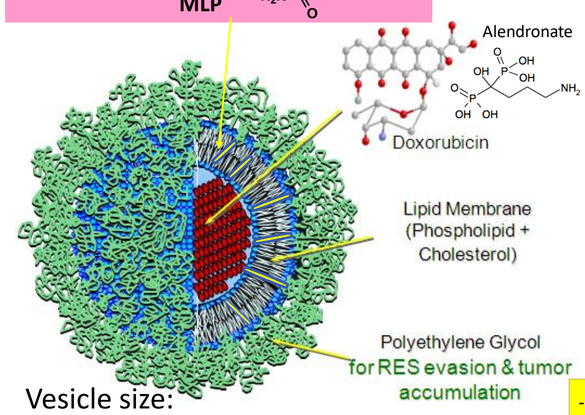
Introduction

- Combination therapies for the treatment of cancer have increased in recent years in an attempt to address the multiple pathways of oncogenesis and cancer cell growth that have been discovered
- Powerful tool for multiple drug delivery: nanoparticles containing co-encapsulated drugs with different mechanisms of action, targeting different pathways of the oncogenic scenario, and with non-overlapping toxicities
- We have shown that Alendronate, an amino-bisphosphonate, is a powerful immune booster that can be co-encapsulated effectively with doxorubicin (JDT, 2016)
- In addition, we have shown that combination therapy with Promitil, a liposomal formulation of MLP (mitomycin-c lipid-based prodrug), and DOXIL is highly effective and probably synergistic in animal tumor models

New formulation for chemo-immunotherapy of cancer: Co-encapsulated Doxorubicin-Alendronate and Mitomycin Lipid Prodrug (PROMALDOX)





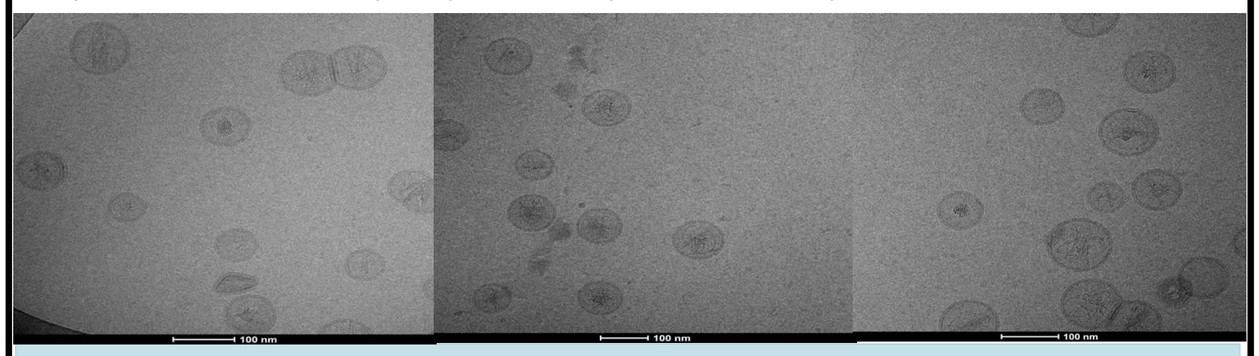
Vesicle size: 90-120nm

Clinical impact:

- Combines three valuable agents (MLP, Dox, ALD) in cancer therapy with synergistic activity
- Immune-mediated anti-tumor effects
- Broaden the spectrum of antitumor activity and circumvent MDR-1 drug resistance
- MLP is currently undergoing clinical testing in a liposome formulation coined PROMITIL®

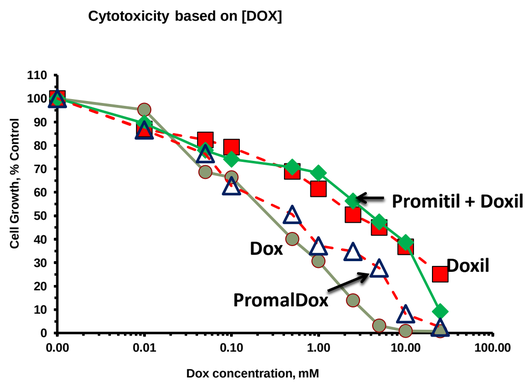
- Convenient Dox: MLP molar ratio (~1.5) for clinical studies
- Great shelf stability at 5°C (>6 months)

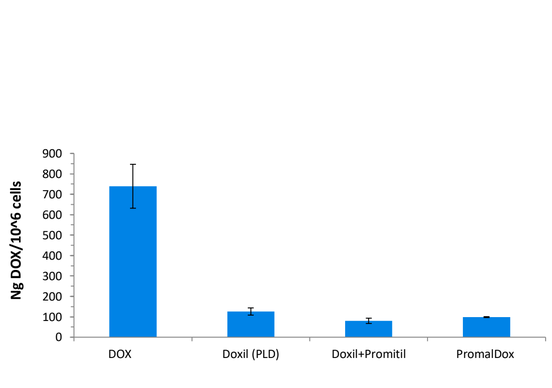
Cryo-TEM Promaldox: precipitates in liposome water phase

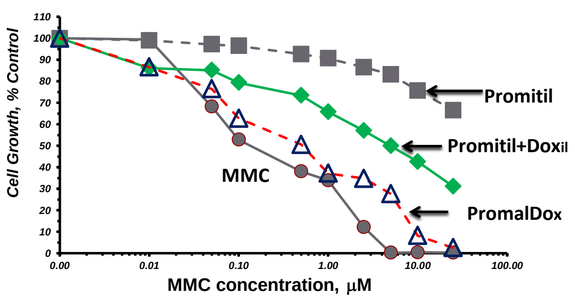


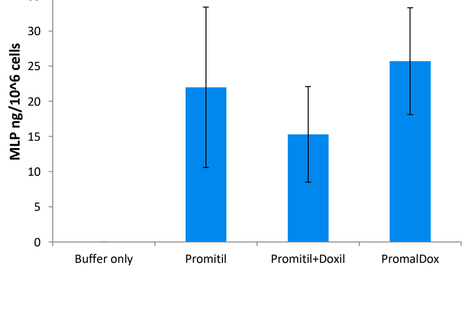
In Vitro Results

Cytotoxic activity of and uptake of Promaldox liposomes



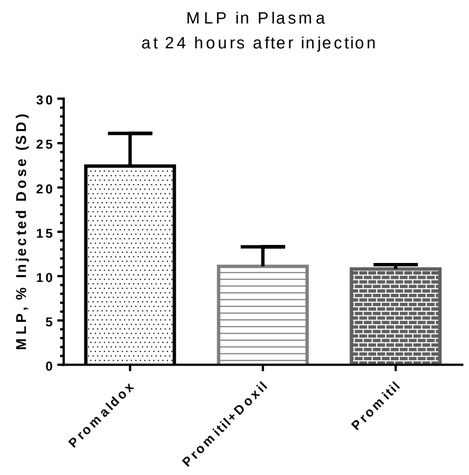


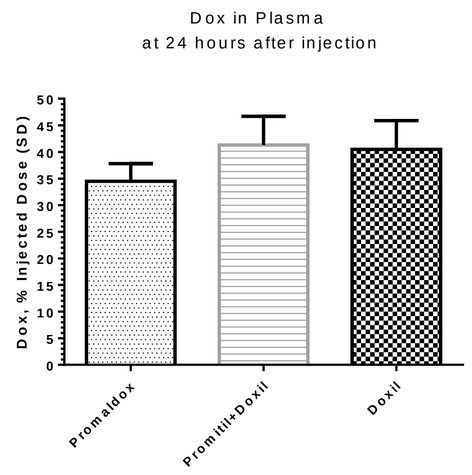




- Similar drug delivery to cells but greater cytotoxicity of Promaldox in N87 gastric human tumor cells

Pharmacokinetic of Promaldox in Mice*



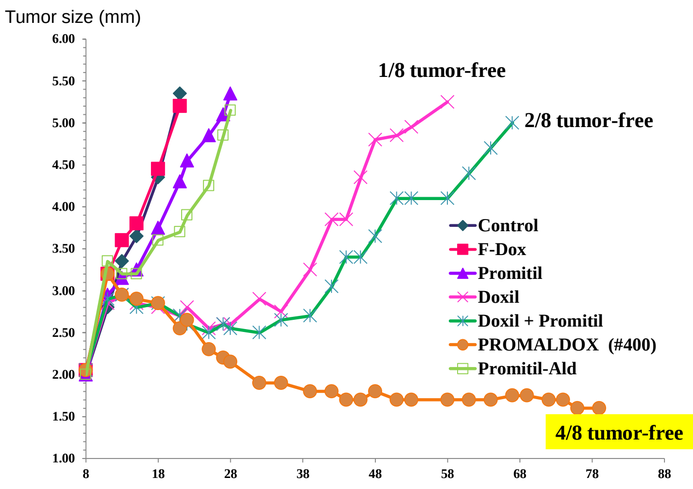


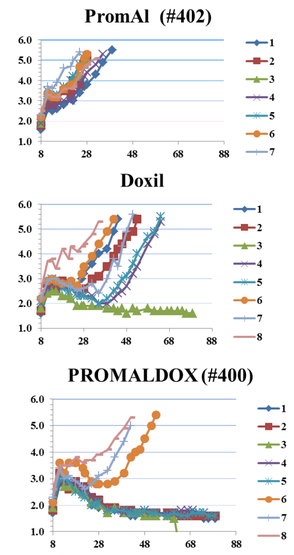
- Greater plasma levels of MLP when present in multidrug liposome (Promaldox) than when in Promitil, indicating greater circulation time and stability.

* BALB/c inbred and Sabra outbred mice

Two In Vivo Therapeutic Studies

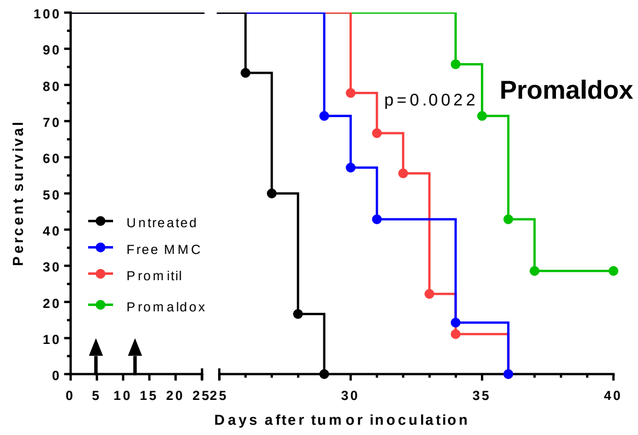
Powerful antitumor activity of Promaldox in the 4T1 breast tumor model





- Potent activity of Promaldox in this aggressive tumor model obtained at low cumulative dose of MLP (1/3 of Promitil)

Greater Therapeutic efficacy of Promaldox in C26 Mouse Colon Tumor Model



- C26 mouse (BALB/c f) colon carcinoma lung metastatic model. Promaldox is significantly superior to all other groups (log-rank test)

Conclusions

- Stable retention of Dox and MLP in Plasma Stability Assays
- Potent in vitro Cytotoxicity against a number of tumor cell lines (greater than Promitil and Doxil combined)
- Long circulation half-life of Dox and MLP (longer than in Promitil)
- Potent in vivo activity (greater than Doxil and Promitil) in mouse tumor models (C26, 4T1)
- Unique and potent multidrug liposome formulation for chemoimmunotherapy of cancer can lead to a promising therapeutic agent with synergistic activity, broad spectrum antitumor activity and reduced toxicity

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