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

Alberto Gabizon1,2,3, Jenny Gorin1,2, Lida Mak2, Dina Tzemach3, Yogita Patil3, Hilary Shmeeda2, Yasmine Amitay4, Patricia Ohana2
1Lipomedix Pharmaceuticals Ltd., 2Shaare Zedek Medical Center, 3Hebrew University- School of Medicine, Jerusalem, ISRAEL

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 DOX 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)

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*

Cryo-TEM Promalodox: precipitates in liposome water phase

In Vitro Results

Cytotoxic activity of and uptake of Promalodox liposomes

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

Pharmacokinetic of Promalodox in Mice*

- Greater plasma levels of MLP when present in multidrug liposome (Promalodox) 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 Promalodox in the 4T1 breast tumor model

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

Greater Therapeutic efficacy of Promalodox in C26 Mouse Colon Tumor Model

- C26 mouse (BALB/c f) colon carcinoma lung metastatic model. Promalodox 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 chemoinmunotherapy of cancer can lead to a promising therapeutic agent with synergistic activity, broad spectrum antitumor activity and reduced toxicity

References