Liposomal Delivery of the Glucocorticoid Dexamethasone Inhibits the Growth of Malignant Bone Lesions from Human Prostate Cancer

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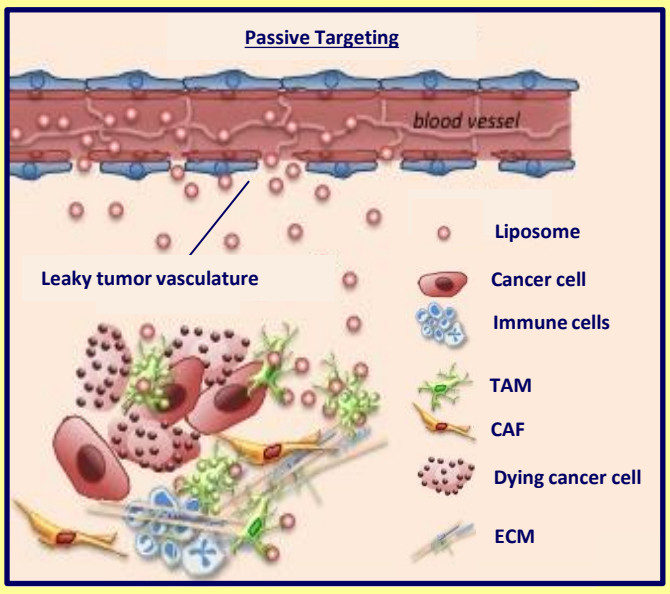
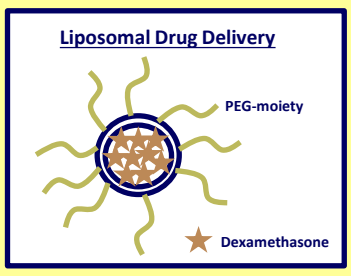
Prostate cancer, tumor-associated macrophages and liposomal drug delivery

During prostate cancer progression, tumor-associated macrophages (TAM) contribute to survival and growth of primary prostate tumors and distant (bone) metastases, e.g. by secretion of IL-6 and TGF-β. Due to the rapid angiogenesis, as a result of tumor- and macrophage-derived factors, the vasculature of prostate tumors and metastases is often chaotic and leaky, a characteristic that can be exploited by liposomal drug delivery (enhanced permeability and retention (EPR)-effect). Liposomal drug delivery has the potential to prolong circulation time, increase tumor localization and to reduce toxicities.

In this study, we present a novel liposomal formulation of anti-inflammatory drug dexamethasone (DEX, clinically used in the treatment of castration-resistant prostate cancer), which efficiently targets prostate cancer lesions in the bone and blocks the activity of TAM.

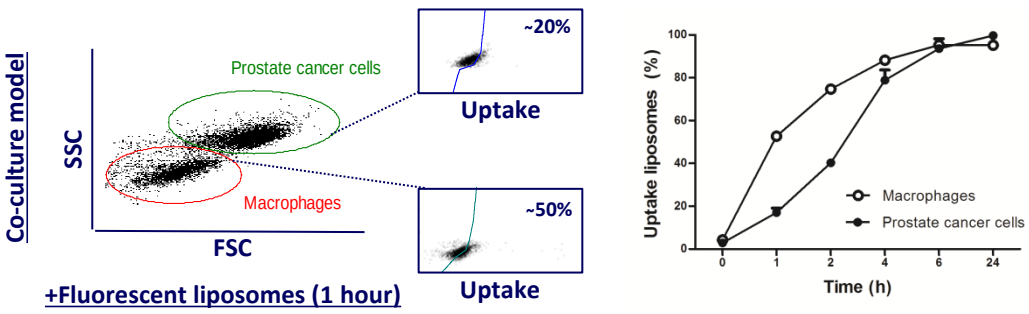


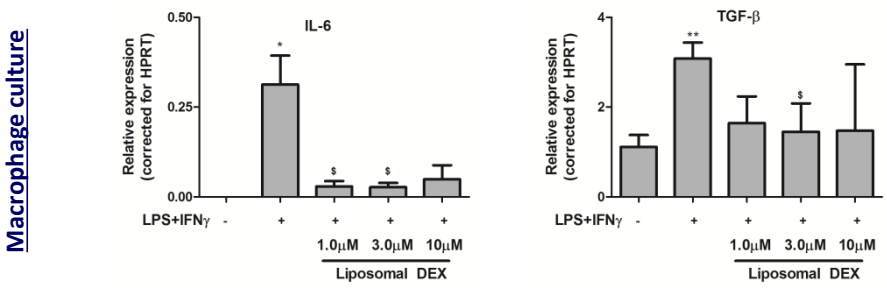


Aim of study

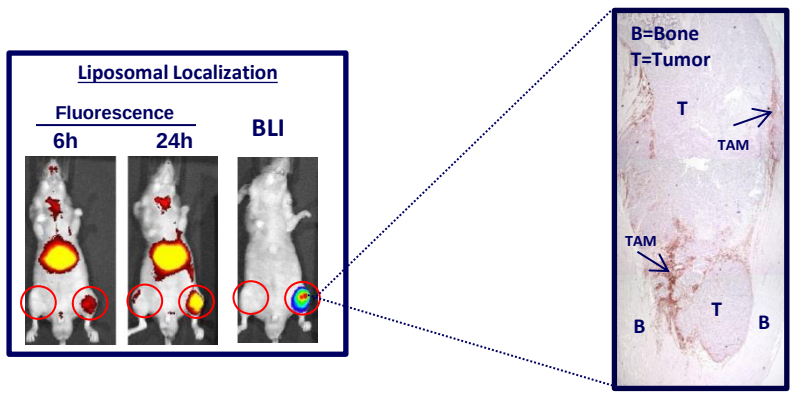
1) Determine the uptake kinetics of liposomes in both tumor cells and macrophages *in vitro*
2) Examine the anti-inflammatory properties of liposomal DEX on macrophages *in vitro*
3) Examine whether liposomes localize efficiently to malignant bone lesions *in vivo*
4) Determine the preclinical anti-tumor potential of liposomal delivery of DEX vs. free administration of DEX
5) Translate preclinical findings to clinical trials in patients with castration-resistant prostate cancer

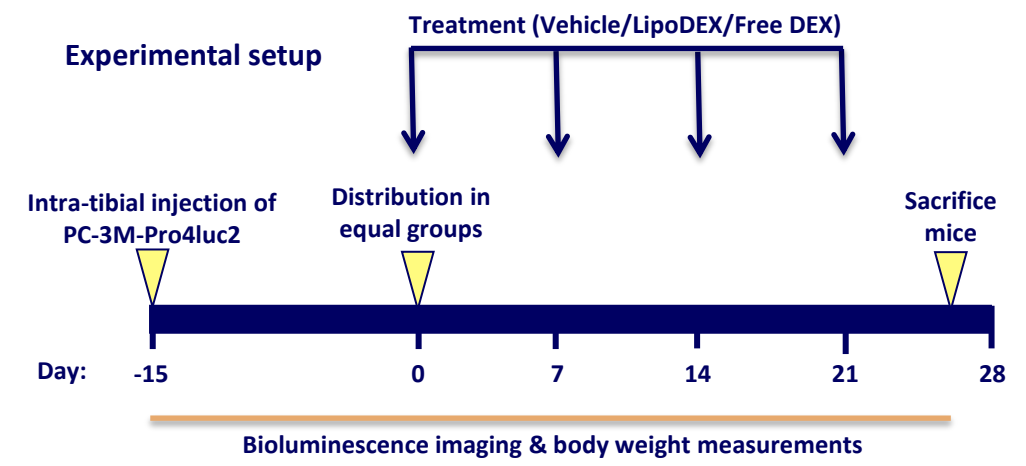
Uptake and anti-inflammatory effects of liposomal DEX in macrophages

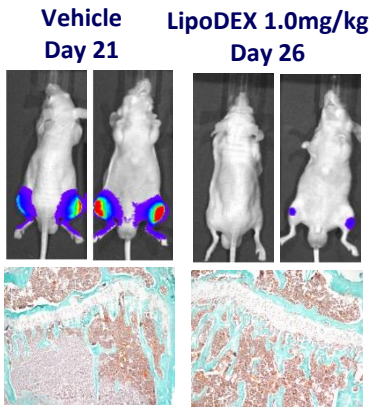


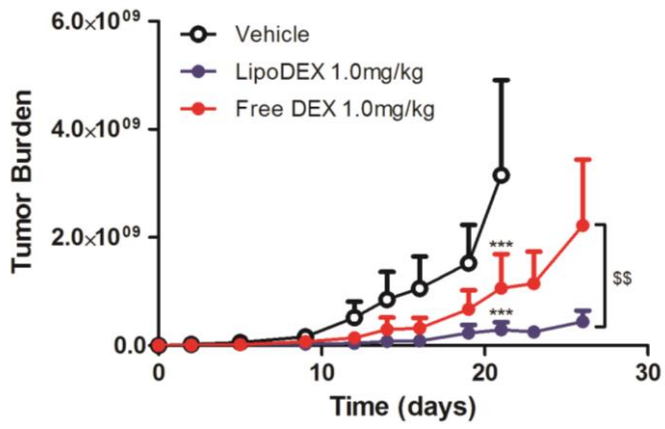


Comparison of liposomal DEX and free DEX in a preclinical model for established bone lesions









Dosage Liposomal DEX	Antitumor efficacy	Liposomal-> Free DEX	Toxicity tumor -bearing mice	Toxicity healthy rats
0.2mg/kg	Yes	Trend	No	Hardly
1.0mg/kg	Yes	p<0.01	Mild and reversible	Mild
5.0mg/kg	Yes	Trend	Severe	Severe

Conclusions

- Liposomal DEX is efficiently taken up by macrophages in a co-culture model
- Liposomal DEX inhibits inflammatory factors in macrophages
- Liposomes localize efficiently at malignant bone lesions
- Liposomal- and free- DEX inhibit the growth of malignant bone lesions and liposomal DEX outperforms free DEX
- Liposomal DEX is well-tolerated at therapeutic dosages
- A phase I trial for the usage of liposomal DEX in castration-resistant prostate cancer patients is currently in preparation

Conflict of interest: GS is on the advisory board of Enceladus Pharmaceuticals. JMM is CEO of Enceladus Pharmaceuticals.