Antitumor efficacy following the intracellular and interstitial release of liposomal doxorubicin

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1. Introduction

PEGylated liposomal doxorubicin (Doxil®) is an FDA approved therapeutic modality for several types of cancer including metastatic breast cancer, ovarian cancer and AIDS-related Kaposi’s sarcoma. Enhancement of drug accumulation and retention within vascularized tumors – a process described by the EPR effect [1] – is among the benefits of this approach. The targeted form of liposomal doxorubicin is expected to become the next generation of this therapeutic modality [2,3]. The targeted approach has been demonstrated [4] to exhibit in vivo superior efficacy against vascularized tumors that is attributed to increased internalization of the delivery carriers by cancer cells comprising the tumors [5]. Interestingly, comparison with identical non-targeted liposomal doxorubicin that exhibits relatively inferior control of tumor growth, demonstrates same accumulation levels for both forms of liposomal doxorubicin within tumors, but significantly lower internalization by cancer cells of the non-targeted modality. Active internalization, therefore, seems to be associated with accelerated intracellular trafficking of doxorubicin in vivo.

At the cellular scale, the above findings point to the same direction with previous in vitro studies demonstrating the importance of intracellular trafficking of doxorubicin in affecting its cytotoxicity. In particular, following selective targeting of and internalization by cancer cells, a triggered mechanism for fast release of doxorubicin from internalized carriers has been correlated with greater accumulation of doxorubicin at the cell nucleus and with greater cytotoxicity [6]. Towards acceleration of intracellular trafficking, triggered release of doxorubicin from internalized liposomes stimulated by the acidification of the endosomal pH has been extensively explored [6–8] and several lipid membrane designs have been developed [9,10]. Intracellularly, not only the rate and extent of release but also the particular pH values at which release starts to occur may significantly affect the intracellular trafficking of the released agent [11]. Especially for the case of