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## Cover Story

## Lessons learned from thermosensitive liposomes for improved chemotherapy

For the last decade the majority of the nanotechnology-based drug delivery systems have been focused on the targeted drug delivery to tumors using nanoparticles. Most studies using small animal xenograft tumor models have shown promising results, i.e., reduction in tumor growth, by nanoparticle systems. Their translation to clinical success, however, has been rare. Since Doxil<sup>®</sup>, a liposomal doxorubicin formulation, has already been in clinical use, further improvement using thermosensitive liposomes has been a good option in developing more effective targeted drug delivery systems. Mild hyperthermia, i.e., treatment of tumors with temperatures between 41 and 44 °C, has shown clinical benefit when used in combination with radiotherapy or chemotherapy [1]. As featured previously as a cover story in this journal, hyperthermia can also benefit nanoparticle accumulation in solid tumors [2]. In theory, as shown in the small animal models, hyperthermia in combination with low-temperature sensitive liposome (LTSL) should work in clinical applications. But the effectiveness of LTSL in clinical trials was less than expected. This may be due to inadequate use of the system, e.g., not achieving the exact temperature necessary for fast drug release in human patients [3]. Developing clinically effective thermosensitive liposome systems requires precise control of the processes of drug delivery to the target tumor, i.e., improved extravasation of the liposomes around tumor tissues followed by temperature-dependent drug release at the right time.

The paper by Professor Gerben A. Koning and his team in this issue suggests a two-step hyperthermia approach to maximize intratumoral liposome accumulation and to trigger drug release from thermosensitive liposomes in tumor interstitium [4]. In the two-step approach the tumor site is first treated with heat at 41 °C for 1 hour to induce hyperpermeable tumor vessels so that the liposome accumulation in tumor tissues can be maximized. After extravasation and penetration of liposomes in tumor tissues has occurred, the second-step hyperthermia at 42 °C for 1 hour triggers intratumoral drug release to achieve the maximum therapeutic effect. This two-step hyperthermia approach is theoretically sound, but it requires a special liposome formulation that can retain doxorubicin at the physiological temperature, but releases its contents at a relatively slow rate during the second step heating period for the maximum therapeutic effect. The Koning group designed traditional fast release and new slow release thermosensitive liposomes using DPPC/DSPC/DSPE-PEG<sub>2000</sub> in molar ratios of 80:15:5 and 55:40:5, respectively.

The study by the Koning group presents a few interesting observations. First, the intratumoral doxorubicin accumulation by the two-step hyperthermia approach using the slow release formulation reached a level comparable to that of the fast release formulation applied with a single hyperthermia 3 hours after the first heating. But, the two-step hyperthermia approach using the slow release formulation was not as effective in inhibiting tumor growth as the intravascular doxorubicin release using the traditional fast release thermosensitive liposome formulation. This indicates that more liposome accumulation around the tumor per se is not enough to achieve the antitumor activity, but creating a free doxorubicin gradient from the tumor vasculature by the intravascular release approach

can be highly efficient. Thus, the presence of drug-containing nanoparticles around a tumor is not directly related to the drug efficacy, as confirmed by the limited efficacy of Doxil in the two-step approach. The penetration depth of liposomes into tumor tissues is also limited, making homogeneous drug delivery to tumor tissues even harder. After all, it is the free drug available to the tumor cells that is important. Second, fine-tuning drug release kinetics for the hyperthermia strategy is crucially important. The slow release liposome formulation for intratumoral release, slowly releasing up to 70% of its doxorubicin content at 42 °C in 1 hour, may have been too slow for the two-step approach to be successful. Clinical applications of thermosensitive liposomes may not achieve desirable outcomes simply because, in clinical practice, a precise local hyperthermia at the tumor may be difficult due to differences in tumor size, location, and perfusion. This observation is consistent with the suggestions made by Professor Needham [3]. There has to be a way to ensure achieving the exact temperature necessary to maximize the benefit of thermosensitive liposomes.

It becomes clear that treating tumors is much more difficult than simply delivering a little bit more drug to the tumor site using nanoparticles. The drug delivery scientists have become complacent in designing various nanoparticle formulations with an unproven assumption that nanoparticles are effective in treating tumors. This decade-old misconception has to be changed to make real progress in the field. The paper by the Koning team is important as it describes a logical two-step hyperthermia approach using nanoparticles and presents the result which was, in a sense, unexpected. Finding new formulations that can be successful in clinical trials requires more extensive communication of unsuccessful results and understanding the possible reasons. The Journal of Controlled Release is committed to provide a forum for disseminating such information.

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