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Cover Story

In vitro and *in vivo* correlation of paclitaxel-loaded polymeric microparticles

In vitro–*in vivo* correlation (IVIVC) is an active area of pharmaceutical research and has important implications in quality control and regulatory compliance [1]. Typical application of IVIVC is to establish the relationship between *in vitro* drug release rate of a dosage form and a parameter indicative of *in vivo* bioavailability, to demonstrate the bioequivalence of the dosage form. The study by Professor Au and her group shows a different type of IVIVC that relates the drug release to the biological activity or pharmacodynamics (PD) of polymeric carriers during intraperitoneal (IP) cancer therapy [2].

IP paclitaxel therapy has shown survival advantage in peritoneal cancer, but has not been widely applied in part due to local toxicity, difficulties in administration, and lack of activity in bulky tumors. As there are no products specifically designed or approved for IP therapy, the current practice is off-label use of intravenous drug solution. However, the rapid clearance of solution from the peritoneal cavity limits the drug exposure and tumor targeting advantage. In addition, the bolus presentation of high drug concentrations tends to cause toxicity. The Au group proposes the following desired properties of controlled-release IP therapeutics: (a) optimized particle size to reduce drainage from the peritoneal cavity and prolong the residence time, while achieving wide distribution within the cavity, (b) polymers that adhere to tumor surface to achieve selectivity, (c) tumor priming to promote penetration into bulky tumors, (d) fractionated drug release to reduce host tissue exposure and toxicity, and (e) sustained release carriers to eliminate the need of frequent treatments and indwelling catheters.

In their earlier studies, the Au group showed that poly(lactide-co-glycolide) (PLGA) microparticles yielded lower local toxicity, deeper tumor penetration, slower clearance from the peritoneal cavity, and higher drug exposure in tumors, as compared with the intravenous paclitaxel/Cremophor micelles solution used off-label in previous clinical studies [3–5]. The current study [2] examines the effect of the properties of PLGA microparticles on *in vitro* paclitaxel release, describes a method to use the *in vitro* release data to simulate the *in vivo* drug dosing rate and cumulative delivery, and evaluates the roles of drug release (rate and extent) in relation to PD.

Professor Au and her team prepared seven paclitaxel microparticles with diverse sizes, polymer inherent viscosities and drug release rates, and selected three for IVIVC evaluation in tumor-bearing mice. These microparticles were given as single agents or in various combinations that yielded a wide range of drug dosing rate and amount, and were compared with the paclitaxel/Cremophor solution. There are several interesting findings. First, the simulated *in vivo* drug release from microparticles correlated with treatment efficacy. Second, the paclitaxel microparticles are generally less toxic and more effective compared with paclitaxel/Cremophor. The IVIVC for survival shows more than twice greater slopes for the regressed lines of microparticles compared to paclitaxel/Cremophor. These results demonstrate the benefits of using controlled release formulations in IP therapy. Third, there is a

temporal component of drug presentation, in addition to the drug dose, that determines the treatment outcome (both toxicity and efficacy). For toxicity, release of >30 mg over 24 h from microparticles was fatal whereas sustained release over days or weeks was tolerated. In comparison, a single 40 mg/kg paclitaxel/Cremophor dose that clears within hours from the peritoneal cavity was not lethal, whereas three weekly treatments were highly toxic. These findings indicate that host recovery from toxicity is determined by both dosing rate and duration of exposure. For survival extension, while either fast or slow release microparticles showed high mg dose efficiency for extending animal survival, tumor-free cures were achieved only with their combinations releasing cumulative amount of at least 40 mg/kg. The synergy of the combination derives from tumor priming by the paclitaxel released from the fast release microparticles, which in turn expands interstitial space and enhances tumor penetration of slow release microparticles. Another interesting finding is the importance of spatial distribution of drug carriers; microparticles with 5–6 μm diameter provided favorable spatial distribution and optimal drug release for IP therapy whereas larger microparticles (48 μm) yielded inferior antitumor activity.

Professor Au's earlier and current studies, taken together, show the successful use of polymeric microparticles to achieve the desired drug dosing rate, target site pharmacokinetics and PD for IP therapy, and highlight IVIVC as an enabling step in the bench-to-bedside translational research of drug delivery systems. This IVIVC study of microparticle formulations is also important for other formulations including various nanoparticle delivery systems. Understanding the key parameters central to tumor treatment is critical in developing clinically significant formulations.

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