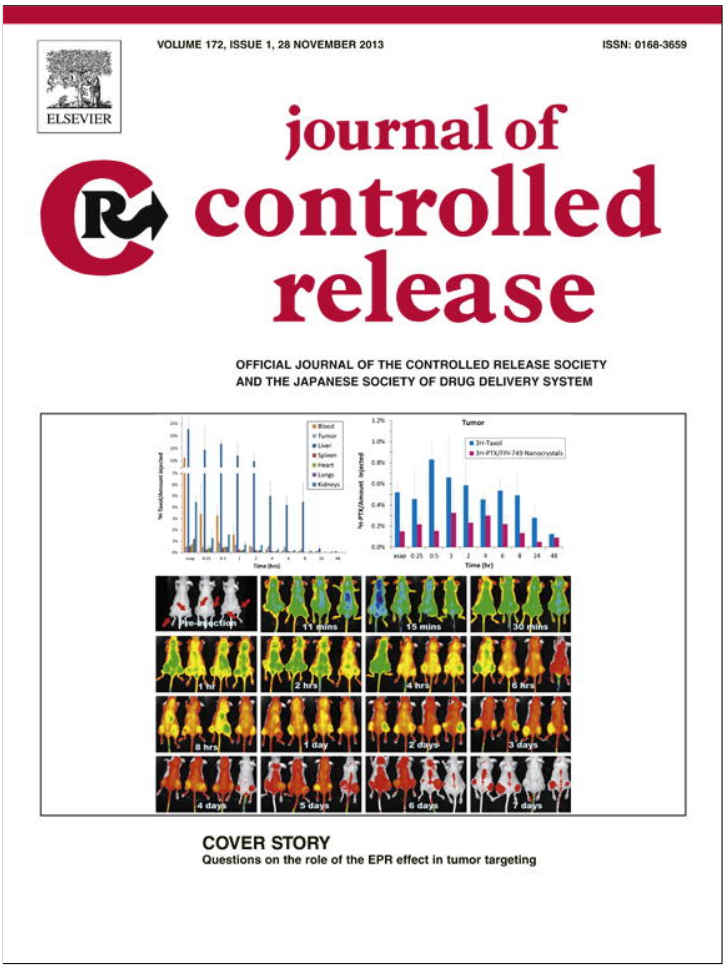

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Cover Story

Questions on the role of the EPR effect in tumor targeting

The enhanced permeation and retention (EPR) effect has been used as a cornerstone in the research on tumor targeted drug delivery. It was comfortably accepted, and conveniently assumed, by many researchers as the *de facto* principle for effective treatment of tumors using nanoparticles. At the height of the nanotechnology fever, the EPR effect was an ideal conduit to channel the potential of nanoparticles to treating tumors, at least in mouse models. It seemed as if the tumor targeting was almost guaranteed if a drug was formulated in nanoparticles. As long as the two terms, "nanoparticle system" and "EPR effect", were combined, the results were predictably good, at least in the mouse xenograft model. The fluorescence intensity at the tumor site was always higher than other organs, typical data supporting the EPR effect. Does that mean it should be taken for granted to draw an equal sign between the EPR effect and effective tumor targeting for any nanoparticle system?

In this issue, Professor Tonglei Li and his collaborators describe their systematic study to examine whether the EPR effect indeed exists. Professor Li's group examined the biodistribution of paclitaxel nanocrystals in tumor-bearing mice [1]. The average size of the nanocrystals was around 200 nm and no surface treatment was done to the particles. They discovered that less than 1% of the total injected paclitaxel reached the tumor site after intravenous injection through the tail vein. The majority of the nanoparticles were actually taken up by the macrophage phagocytic system (MPS). In the study, tritium-labeled paclitaxel was included in their production of nanocrystals from a solution. Thus, the exact quantity of paclitaxel reaching the target tumor was analyzed accurately by scintillation counting. Taxol®, which was used as a control, also showed less than 1% accumulation in the tumor. Both formulations demonstrated similar anticancer efficacy, but the nanocrystals seemed to elicit less systemic toxicity despite a significant liver uptake. Literature information indicates that paclitaxel in Taxol® is likely to be delivered as the micellar form [2]. The extremely low amount, *i.e.*, $<1\%$ of the total administered dose, delivered to the tumor site by both Taxol® and nanocrystals raised a question on the significance of the EPR effect.

Professor Li and his colleagues further conducted bioimaging studies of the treated animals since their nanocrystals also physically integrated fluorescent molecules. The fluorescent intensities of the mice at different time points and dissected tissue samples deviated dramatically from the biodistribution results. The images show significant brightness at the tumor site, especially after 48 h of the treatment, suggesting large accumulation of dye molecules. Given the outstanding discrepancy between the biodistribution and bioimaging results, the authors suspect that the fluorescence dye might exhibit different biodistribution behaviors, especially in blood, as compared with the drug and drug nanocrystals. The dye molecules could be released from circulating nanocrystals or even nanocrystals trapped in the liver. Because the tumor was implanted under the skin where no other high blood-flowing peripheral organs exist, the fluorescent intensities became deceptively brighter and eye-catching. Using bioimaging data to demonstrate tumor targeting of a drug delivery system may only add to our misconception of the EPR effect.

There are also a few other papers in this issue discussing the delivery of nanoparticles that further underscore the complexity. The paper by Lee et al. points out, based on bioimaging data, that their nanoparticles "showed great tumor accumulation based on the EPR effect" [3]. Often, the biodistribution data are reported as the drug concentration normalized by the weight of a reported organ (*e.g.*, the papers by Zhang et al. [4] and by Allmeroth et al. [5]), making it difficult to comprehend the overall distribution among organs and tissues.

The paper by the Li group on the paclitaxel nanocrystals and others on nanoparticle-based drug delivery systems brings an important question on the validity of the fluorescence imaging studies and the presence of the EPR effect. The current paradigm of targeted delivery to tumors using the mouse xenograft models requires careful reexamination. Recent literature data indicate that nanoparticles do not really increase the amount of the drug delivered to tumors, but the toxic side effect seemed to be reduced. In fact, as pointed by the Li group, it may be more productive if the nanoparticle research focuses on reducing the systemic toxicities and balancing the biodistribution in health organs and tissues. After almost two decades of blind belief on the EPR effect, it is time to think outside the box to really move the tumor targeted drug delivery forward.

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Kinam Park
Purdue University,
Departments of Biomedical Engineering and Pharmaceutics,
West Lafayette, IN, USA
E-mail address: kpark@purdue.edu.

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