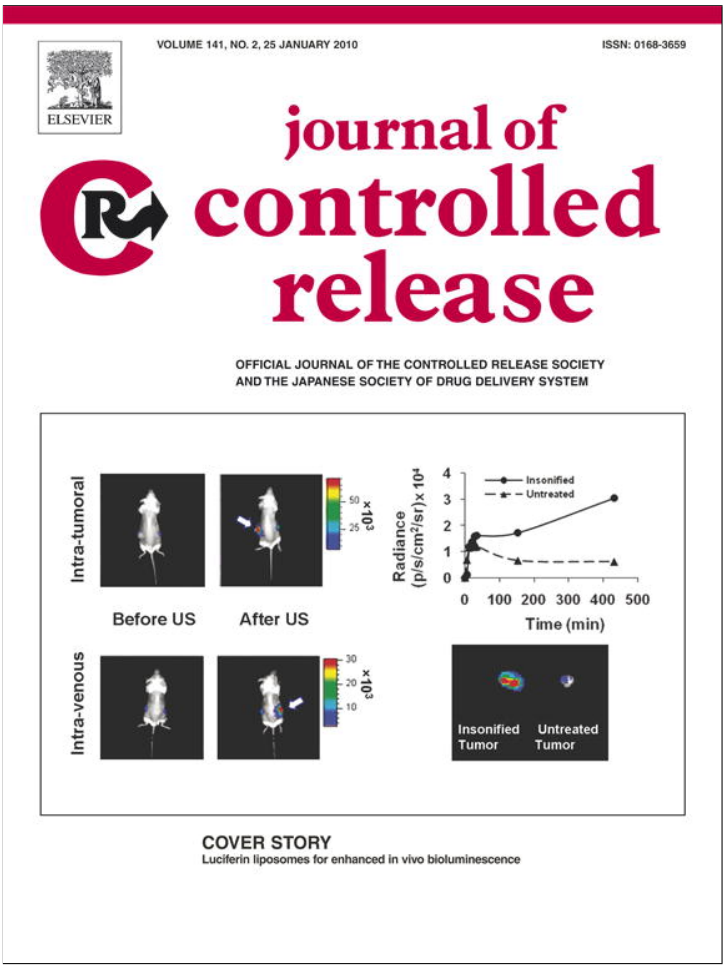

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Cover Story

Luciferin liposomes for enhanced *in vivo* bioluminescence

Drug targeting has been an ultimate, but elusive, goal in drug delivery, and a large number of drug delivery vehicles have been developed in a hope to accomplish it. One of the difficulties in studying drug targeting is the lack of appropriate experimental tools to monitor drug distribution and delivery to the target site in real time. The development of imaging strategies for minimally-invasive measurement is of increasing importance not only for studying drug targeting but also for fundamental discovery. Recently, bioluminescence imaging has proven very useful in studying various molecular and cellular processes *in vivo*. Bioluminescence refers to the production of visible light by chemical reaction occurring in living organisms. One of the well known methods for bioluminescence imaging is based on emission of light by luciferase-catalyzed conversion of luciferin to oxyluciferin. Thus, bioluminescence imaging makes it possible to track the relative amounts and locations of luciferase *in vivo*, mainly in small animals, by detecting the light transmitted through a small animals' tissue. Bioluminescence can be used as a tool for studying image-guided drug delivery.

In the paper published in this issue, Professor Ferrara and her group have examined sustained delivery and intracellular targeting using bioluminescence imaging [1]. Liposomes were loaded with luciferin, which was used as a surrogate nano-cargo. Using luciferin is advantageous because of the absence of background radiance, as compared with fluorescent probes. Furthermore, the induced radiance requires an enzymatic reaction between luciferin and intracellular luciferase, and therefore confirms intracellular delivery. The group accomplished two major goals: sustained delivery of luciferin and systemic delivery of this *encapsulated* small molecule to the intracellular target. Luciferin is widely used to elucidate biological mechanisms, yet the rapid clearance is limiting in longitudinal studies. Professor Ferrara's group achieved sustained bioavailability of luciferin by actively loading it into long-circulating liposomes. After injection into the blood, an initial burst of release was observed followed by sustained delivery to a range of tissues in transgenic animal models. The pharmacokinetics of luciferin within long-circulating liposomes was contrasted with encapsulation within temperature-sensitive liposomes and with free luciferin, demonstrating the decreased clearance rate achieved with the long-circulating particles.

The encapsulated luciferin was also harnessed to evaluate ultrasonic activation of temperature-sensitive nanoparticles, thus realizing the goal of image-guided local drug delivery. After insonifying one of two bilateral tumors containing *interstitial* temperature-sensitive particles, the locally-enhanced radiance in the insonified region verified immediate release of the luciferin in the desired region of interest. Alternatively, while cholesterol-rich liposomes were *circulating*, local heating resulting from tumor insonation increased accumulation and tumor radiance over a period of hours. Thus, at least two modes of image-guided delivery can be advanced with the use of a luciferin cargo; image-guided release and locally-enhanced accumulation can both be visualized and quantified. The development of methods to co-optimize particles and activation methods, such as those demonstrated here, has the potential to rapidly advance image-guided therapy, and ultimately drug targeting.

Reference

[1] A. Kheirolomoom, D.E. Kruse, S. Qin, K.E. Watson, C.-Y. Lai, L.J.T. Young, R.D. Cardiff, K.W. Ferrara, Enhanced *in vivo* bioluminescence imaging using liposomal luciferin delivery system, J. Control. Release 141 (2009) 128–136.

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