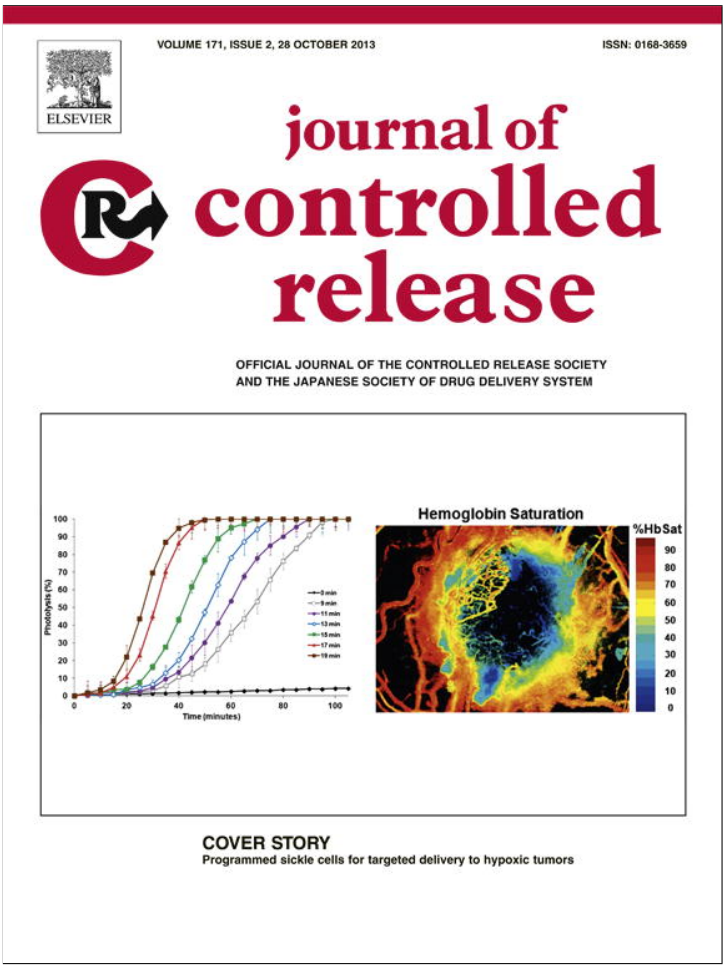

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Cover story

Programmed sickle cells for targeted delivery to hypoxic tumors

Systemic administration of cytotoxic drugs is common in cancer therapy. Drug carriers are designed to favorably alter the delivery and biodistribution of drugs, thereby improving their toxicity profile and enhancing therapeutic efficacy. Drug carriers currently approved for clinical use in cancer generally are submicron particles that deliver drug through blood circulation and subsequent extravasation to the tumor site. Despite development of numerous nanoparticulate drug carriers the therapeutic results have not met expectations or attained their theoretical advantages over use of free drug. Some benefits observed with certain carriers, e.g., liposomal doxorubicin in breast cancer, are due to reduced toxicity, rather than by the enhanced efficacy, by the nanoparticulate formulations. Given lackluster results with common approaches based on nanoparticles, new approaches for drug carriers are warranted [1].

In this issue, Dr. Brian Sorg and his colleagues, building on the previous work by Dr. David Terman and his team [2], introduce light-activated sickle red blood cells (SSRBCs) as novel hypoxic tumor-targeting controlled release drug carriers [3]. Normal RBCs have been proposed as carriers for various therapeutic agents over the years. RBCs have a number of positive characteristics as drug carriers, including long *in vivo* circulation times, the ability to carry a wide variety of compounds (small molecules, genes, proteins), a secure partition between the RBC interior and external environment, and a large drug loading capacity [4]. Normal RBCs, however, have limitations for cancer therapy in that they lack endogenous tumor targeting capabilities, and thus, they remain in general circulation as slow release vehicles. Carrier controlled release by physical stimulus has been widely studied, and popular methods include application of directed energy such as light, ultrasound, and heat (e.g., radiofrequency heating). However, these directed energy methods as currently employed have limitations in treating advanced disseminated and metastatic disease, because they require direct application of energy to the carriers within each individual tumor. For this reason, those methods will only be effective for tumors at a tissue depth within reach of an applied energy field of sufficient strength to trigger release [5]. The authors of the paper in this issue combined two novel innovations in their study [3]. First, they employed SSRBCs as drug carriers, rather than normal RBCs. SSRBCs express multiple adhesion receptors which bind cognate ligands expressed in hypoxic tumor microvessels, a significant feature as hypoxic microvessels may be a common target for many solid tumors. Second, they used a variation of light-triggered release that enables light activation *ex vivo* under controlled conditions to initiate carrier photo-oxidation immediately prior to systemic administration. This method eliminates the need for direct activation of carriers within each individual tumor and may enable controlled release in more advanced disseminated and metastatic disease regardless of tumor location.

The SSRBCs retained their tumor accumulation properties after loading of a model drug (calcein) and accumulated more in tumors than adjacent tissue and organ sites like liver and spleen. SSRBCs reached significant tumor accumulation about 12–24 h after systemic administration. Using the *ex vivo* light activation method, calcein release was controlled and coordinated with SSRBC tumor accumulation such that 50% release of calcein from SSRBCs occurred at about 15–16 h after their activation and administration. Microdialysis confirmed 3–4 fold greater tumor deposition of calcein in mouse tumors from the light activated SSRBCs compared with equal doses of calcein-loaded light activated normal RBCs, calcein-loaded SSRBCs that were not light activated, and free calcein. These results clearly demonstrate the benefit of combining tumor targeting and controlled release capabilities in drug delivery vehicles.

Much work remains to be done with this technique, including demonstration of enhanced delivery of actual anti-cancer agents, a measurable therapeutic response, and long-term toxicity studies. Additionally, the technique should be compared with currently approved drug carrier formulations. However, this study demonstrates a viable alternative to current drug carrier approaches that may lead to new types of delivery vehicles and controlled release methods that are needed in the field. The most unique aspect of this approach is that SSRBCs can be programmed to undergo delayed photolysis by controlling the *ex vivo* photoactivation time. The ability to release the loaded contents after a predetermined time delay can be a highly useful tool in itself and as a combination with other drug delivery techniques.

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