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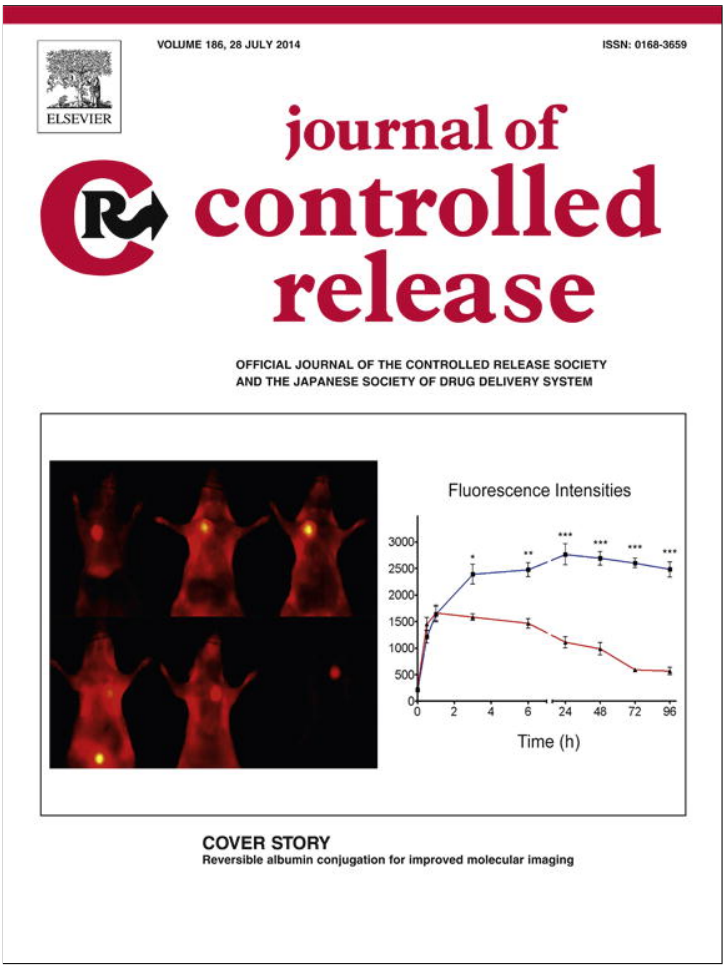

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Cover story

Reversible albumin conjugation for improved molecular imaging

The field of molecular imaging has been evolving to enhance the visualization of disease-related pathophysiological processes on the cellular and sub-cellular level for more than a decade now. It relies mainly on the availability of specific probes that address target structures which are expressed in diseased tissues. The applied molecular imaging probes, however, are often found to be rapidly cleared from the circulation, limiting the delivery to the target site, or to display disadvantageous metabolic behavior. This results in poor imaging performance with respect to signal-to-noise ratio (SNR) and only a few new probes have actually reached clinical trials [1]. Improving the SNR can be achieved by, e.g., enhancing the accumulation of an imaging probe at receptors in the target tissue.

The work of Dr. Höltke and his colleagues presented in this issue focuses on optimizing the bioavailability of a probe by exploiting the inherent circulatory transport mechanisms of albumin [2]. Human serum albumin (HSA) has been playing an increasingly important role as a drug carrier in clinical settings, and albumin-bound drugs have been successfully developed for treatment approaches. The use of HSA in molecular imaging approaches has recently been reviewed [3]. The discussed optical probes in the article, however, are restricted to covalently bound examples. This leaves a number of concerns, e.g., reduced bioactivity after chemical grafting, low tissue penetration, and altered fluorophore behavior. The work by the Höltke team describes the chemical modification of an existing fluorescent probe by a hydrophobic albumin affinity tag which was used in Vasovist™, a magnetic resonance contrast agent. A fluorescent endothelin-A receptor (ET_AR) imaging probe was modified by attaching the albumin affinity tag and labeling the conjugate with the fluorescent dye Cy 5.5. The target binding potential of the new probe was tested *in vivo* by the molecular imaging of murine xenografts. The probe with the albumin affinity tag showed a much higher accumulation in target tissue than the control. The probe also showed a reduced renal clearance and a significantly prolonged circulation time. This resulted in a significantly higher signal intensity at the target site and a higher SNR between 3 h and 96 h after injection. Additional experiments were performed by injecting Cy 7-labeled bovine serum albumin and a synthesized albumin-binding control probe containing the affinity tag but not the receptor ligand. Both experiments did not show a marked accumulation of a fluorescent signal in the tumor lesion. The enhanced permeability and retention (EPR) effect has often been discussed as a factor influencing tumor targeting properties of drugs and diagnostics, including those that bind to albumin. The study on the reversibly labeled albumin accumulating in tumors, however, emphasizes the fact that tumor xenografts do not necessarily show a significant EPR effect [4]. The fluorescence signal of the tumor site may exceed that of the muscle, but only by a very small margin. The EPR effect, if there is any, may play only a very minor role in probe accumulation, at least in the used xenograft model.

The figure on the cover page of this issue depicts differences in imaging performance of the compared ET_AR-tracers. The albumin-binding property of the new tracer enhances the tumor fluorescence significantly in a sustained manner. The presented approach of reversibly attaching a probe to serum albumin has been proven to be a reliable tool for the pharmacokinetic modulation of molecular imaging tracers. This may not only result in an optimized SNR of imaging probes for more precise target characterization, but may also serve as a method to optimize the distribution of small molecular drugs in therapeutic applications. Considering the fact that many drugs bind to albumin as soon as they enter the blood stream, the approach by the Höltke team has been long overdue. This simple, and yet elegant, approach will benefit the field of nanomedicine which has been suffering from its limited success in clinical settings. It also emphasizes the need for more elaborate preclinical models and technical instruments in our efforts of translation from mice to men.

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