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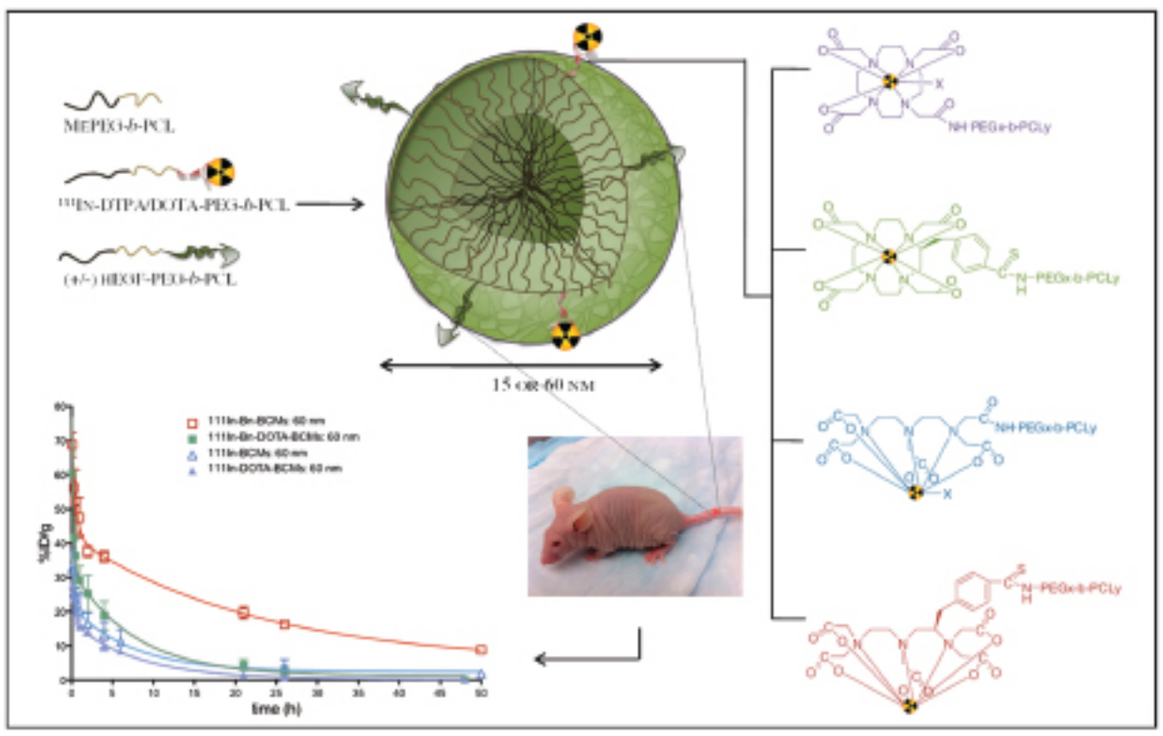

COVER STORY

The optimal formulation variables for tumor targeting

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Cover story

The optimal formulation variables for tumor targeting

Interest in the design and development of drug delivery technologies for selective delivery (i.e., targeted delivery) to solid tumors continues to increase. For applications in drug delivery, nanovehicles, such as liposomes, block copolymer micelles and polymer–drug conjugates, have shown to be viable technologies that result in significant improvements in tumor accumulation and/or a reduction in systemic toxicity [1]. Typically, the increase in tumor accumulation by targeted nanovehicles is more than two-fold and up to several-fold. This increase, however, is understood in the context that the amount of the delivered nanovehicles is still less than 5% of the total administered dose. Thus, beyond the progress that has been made there is continued interest in achieving more selectivity as well as delivery to cellular and intracellular targets. Achieving systemic targeting is one thing and achieving subsequent intracellular targeting is another. These are challenging goals due to the need to achieve a prolonged blood circulation time which is necessary to exploit the EPR effect, while also overcoming the numerous transport barriers encountered at the tumor site [2,3].

It is well known that the physico-chemical characteristics (i.e., size and morphology) of drug delivery systems have a significant influence on their pharmacokinetics and biodistribution. The impact of so-called active targeting moieties (i.e., moieties that bind to the receptors on the target tumor cells), in particular low molecular weight ligands, is less clear. This is because the ligand–receptor interaction occurs only after a drug delivery system is delivered to the target tumor. Furthermore, it has been assumed, in the absence of any experimental data, that an increase in the density of the targeting moiety results in higher accumulation at the target site. This is important information in the design of targeted drug delivery systems. In this issue, Professor Christine Allen and her coworkers have shown that an increase in the density of a targeting moiety at the surface of the delivery system is not always better [4]. This is because it can result in accelerated removal of the system from the circulation and a concomitant decrease in tumor deposition. This is information that is critical in the design of targeted delivery systems. It is counter-intuitive, but it actually makes sense. The density of the targeting ligand must be optimized to benefit from its presence at the vehicle's surface.

Overall, the influence of formulation variables on the distribution of delivery systems in vivo is complex and generally requires assessment in vivo given the limited ability to make reliable predictions based solely on findings from in vitro evaluation. In fact, it is rather impossible to evaluate the in vivo targeting ability based on in vitro studies where the target cells are directly exposed to the nanovehicles (e.g., in a Petri dish). In recent years imaging methods have been used to assess the distribution of nanovehicles in vivo. The nanovehicles can be labeled with radionuclides or contrast agents that permit non-invasive, image-based detection of their distribution [5,6]. This integration of imaging in drug delivery has also prompted an interest in the development of theranostics and therapeutic–diagnostic pairs, with a goal towards improving patient stratification and the implementation of personalized medicine [7]. For imaging by magnetic resonance (MR), positron emission tomography (PET) and single photon emission computed tomography (SPECT), labeling of the delivery system is often achieved via chelation of gadolinium for MR imaging or radionuclides for PET and SPECT imaging (e.g., Copper-64, or Indium-111 (^{111}In), respectively) to bifunctional chelators that are conjugated to the surface of the delivery system. The high sensitivity of PET and SPECT enables the use of limited levels of radionuclide and in turn a low density of bifunctional chelator to be present for effective imaging. However, as shown with active targeting ligands, even minor components present at the surface of a delivery system can have a profound impact on the distribution of the delivery system in vivo. This is understandable considering the fact that labeling any molecule with a fluorescent probe is known to alter the properties of the molecule of interest. Professor Allen and her team confirmed that the nature of the bifunctional chelator employed for radiolabeling has a significant influence on the pharmacokinetics and tumor deposition of the delivery system. They highlighted that the choice of bifunctional chelator to be employed for labeling is a formulation variable that must be optimized for the successful design of theranostic nanovehicles.

The design of radiolabeled nanovehicles is of interest and importance not only for applications in image-guided drug delivery but also molecular imaging and radiotherapy. There are a complex array of formulation variables that must be considered in the successful design of these systems with even minor components making a significant impact on fate and therefore effectiveness. While it is not easy to label the nanovehicles, it is critically important to acknowledge that any modification of the nanovehicle surface will have to be optimized. It cannot be over-emphasized that an increase in the ligand concentration does not necessarily result in higher accumulation at the target site. Like many things in life, moderation seems to be the best even in ligand-based targeted drug delivery.

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

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