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Cover Story

A microfluidic system for evaluating drug delivery to solid tumors

Currently, tumor-targeted drug delivery systems are usually tested in xenograft mouse models and genetically engineered mouse models. Extensive studies to date, however, have shown that the data from these models are not correlated with the clinical outcomes. Promising nanoparticle formulations from mouse studies failed to reproduce the results in clinical studies. This translation problem may be, in large part, due to the shortcomings of the mouse models, such as lack of correlation across species, challenges of including the immune component, and slow and variable tumor development often marred by artificial drift. The absence of correlation between small animal models and clinical efficacy has stimulated the drug delivery scientists to find alternative methods that can more accurately predict the clinical efficacies. Recent advances in 3-dimensional (3D) microfluidic devices provide a partial solution to finding *in vitro* systems that can adequately represent tumors in human patients [1–3]. Dozens of microfluidic devices are commercially available for separating circulating tumor cells, tumor cell migration study, and testing drug efficacy under flow conditions. Only a few, however, feature separate channels for blood flow and 3D culture of tumor cells.

The paper by Dr. B. Prabhakarpandian and his colleagues in this issue [4] demonstrates *in vitro* microfluidic methodology for screening the efficacy of drug delivery vehicles and drugs. They reproduced microvascular networks from *in vivo* images to create the *in vivo* tumor microenvironment encompassing real-time visualization of circulatory flow in the vessels, transport across the vessel walls between the vascular and tumor cells, and delivery to 3D culture of tumor cells. The study tested two gene delivery systems, polyethylene glycol–polyethylenimine–cholesterol (PPC) and low molecular weight linear polyethylenimines (Express-In), for their ability to transfect a 3D cervical cancer model. In the Prabhakarpandian team's microfluidic device, the vascular channel for culturing endothelial cells is separated from the tissue compartment for culturing tumor cells to mimic extravasation of drug delivery systems from the blood vessel. The presence of a separate vascular channel is important, as it provides information on the impact of interaction between drug delivery systems and serum proteins. For example, Express-In showed significant aggregation in the vascular channel, while PPC remained relatively aggregation-free. The developed synthetic tumor network device can be used to study drug delivery vehicle transport mechanisms, drug–cell interactions, tumor transfection, and tumor–endothelium interactions.

Although microfluidic devices present unique advantages over testing static 3D tumor spheroid cultures, further advances need to be made for practical applications as intended. It is important to remember that any new approach comes with limitations. One of the main limitations in studying drug delivery to tumors using microfluidic systems, or any systems for that matter, is our inability to closely mimic the tumor microenvironment in human patients. Delivery of a drug to the tumor region is one thing, and maximizing the drug effect against tumor cells is another. The tumor microenvironment comprises a highly heterogeneous mixture of tumor and stromal cells embedded in an extracellular matrix with many cytokines, growth factors, inflammatory cells and macrophages. Recreating such complex tumor microenvironment requires more advanced microfluidic systems that can allow growth of tumor and stromal cells in an artificial extracellular matrix.

There is no doubt that progress in microfluidic systems will be made, but the device engineering progress has to be accompanied with the progress in our understanding of the complex nature of the tumor microenvironment. As the technological and scientific improvements mature synergistically, the data obtained using 3D microfluidic devices will become more clinically relevant.

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Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu

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