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Cover Story

Zebrafish as a screening tool for the systemic circulation of nanoparticles

During the last few decades, a vast amount of nanotechnology-based drug delivery systems has been developed, but the clinical translation of the preclinical data, obtained mostly from xenograft mouse models, has been disappointing. There are many reasons for the huge gap between the technical and clinical development of so-called nanomedicine formulations. To date, many approaches have included formulation development based on inadequate targeted delivery concepts and inadequate preclinical test models [1–3]. Currently, the main concept of nanomedicine is that nanoparticulate drug delivery systems may decrease off-target effects and increase target tissue concentrations. This concept, however, has not met the initial expectations on nanomedicine. It is time to critically examine the current strategies in nanomedicine development. The useful answers can be found only after the right problems are identified. One such problem is whether the preclinical models, in particular xenograft mouse models, are the right models for finding the right delivery systems. Suitable preclinical models that can predict drug pharmacokinetics and tissue distribution of potential formulations are necessary.

The paper by the Huwyler and Witzigmann team in this issue focuses on the zebrafish model as a vertebrate screening tool to study the systemic circulation of nanoparticles [4]. This model was developed to address several of the problems with current preclinical models. The zebrafish has been used as a model organism in genetics, developmental biology, and toxicology. The present manuscript has employed this organism for the first time as a model in development of nanoparticulate formulations.

To validate this approach, Sieber et al. injected small volumes of fluorescent nanoparticles (i.e., 1 nL) into transgenic zebrafish embryos expressing green fluorescent protein (GFP) in their vasculature b dgbh. After specific time points, the circulation and extravasation behavior of single and multi-component lipid formulations were qualitatively and quantitatively assessed. Importantly, the circulation behavior of nanoparticles in zebrafish embryos was predictive for the pharmacokinetics in rodents. This approach is different from current screening strategies, which follow a more traditional pattern of organization based on *in vitro* cell-culture screening and *in vivo* studies in rodent. The transition from *in vitro* experiments to the *in vivo* assessment in rodents is cost and time intensive. (Whether the rodent models for testing nanoparticulate formulations provide information that is relevant to human applications is a separate matter). Thus, it is difficult to screen a large number of nanoparticles using small animal models and to select promising lead formulations.

The study by the Huwyler and Witzigmann team presents several interesting observations, which could improve the current approach of nanomedicine development. First, different nanoparticles can be screened *in vivo* in an early stage of development in a time- and cost-efficient manner using image-based methods. The blood circulation patterns are established just 1 hour post injection. This offers the possibility of an almost immediate first assessment of particle performance *in vivo*. In addition, this model offers a high throughput optimized and parallel screening process, since many fish embryos can be processed within a short period of time. Second, the zebrafish model can be used as a predictive tool. The circulation and extravasation of various liposome formulations containing lipids with different transition temperatures, varying cholesterol content or PEG shielding were assessed. Notably, the nanoparticle concentrations in the zebrafish circulation were correlated to their pharmacokinetic parameters in mice and rats. Third, the zebrafish presents an alternative vertebrate screening model, which can reduce the number of experiments in higher vertebrates. A large number of nanoparticles can be screened in a biological environment, and only promising nanoparticle formulations will be further investigated in higher animals.

The usefulness of the zebrafish model in predicting the efficacy of nanoparticulate formulations, or any formulations under development, in humans will be determined in time. It may show only partial relevance or more than expected. Regardless, the importance of the zebrafish model is that it is a new attempt to find alternative models that drug delivery scientists can test. Instead of trying the same model over and over again, especially the models that turned out to be mostly irrelevant to human applications, the Huwyler and Witzigmann team came up with something new and innovative. If the new model works, we can keep refining it, and if not, we can search for other models. The authors have shown that we can explore something unknown and bold in search of better models that can predict clinical outcomes.

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