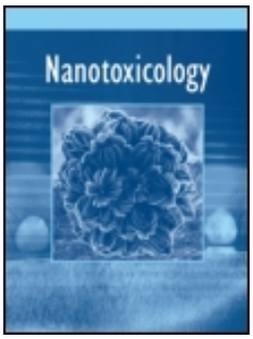

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LETTER TO THE EDITOR

Exploring the interactions of nanoparticles with multiple models of the maternal–fetal interface

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A team exploring uncharted terrain might consist of both a helicopter pilot and a hiker on the ground. Although the pilot can scan a vast segment of the region in a short amount of time, many details of the land cannot be discerned from above. The hiker, on the other hand, is able to gather various particulars of plant life and specifics about the soil, but in terms of distance covered, his or her progress is comparatively slow. Despite the advantages and disadvantages of each member of the team, both serve an important purpose. An expedition carried out by the hiker alone would take too much time, and an analysis that relied only on the chopper's flyover would be incomplete. By working together and with good communication, their energies can be focused on the most intriguing opportunities before them.

Nikitina et al. have highlighted an important area of research that is in need of exploration. The potential benefits and risks of nanoparticles in pregnancy have implications not only for the mother's health, but also for fetal well-being. The developing fetus is listed among the most vulnerable members of the human population (Saunders, 2009), especially since what happens in the womb can affect long-term health (Barker & Thornburg, 2013). Although the presence of nanoparticles in the circulation may be the result of unintentional environmental or occupational exposure, there may also be opportunities to improve maternal and fetal therapy by means of nanoparticle-mediated drug delivery (Ali et al., 2013; Rytting & Ahmed, 2013).

Interactions of nanoparticles with the maternal–fetal interface raise questions regarding transport and toxicity. Models for exploring the distribution of nanoparticles across the placenta include BeWo b30 cells and the *ex vivo* dually perfused human placental lobule. Of these two models, the perfused human placenta is the better representation of the *in vivo* situation, as it retains the complete set of placental organization. Nevertheless, it is a time-consuming method requiring fresh placental tissue, and many experiments are nullified due to high leakage and failure rates (Mathiesen et al., 2010). While perfusions with full-term placentas cannot provide data regarding early gestation, placentas obtained following preterm deliveries may not represent normal tissue (Nanovskaya et al., 2008). The BeWo choriocarcinoma cell line is of human trophoblast origin and serves as an *in vitro* model of the rate-limiting barrier for maternal–fetal exchange (Rytting et al., 2007). Although the BeWo cell model lacks spontaneous syncytialization, connective tissue and endothelium present in placenta, it is a more convenient experimental model which can produce transport and metabolism data more rapidly than the perfusion model. Readers are referred to the report of Poulsen et al. (2009) for a thorough discussion of the advantages and disadvantages of both experimental models.

We previously compared the maternal-to-fetal transport of four compounds by both placental perfusion and the BeWo cell model, and we observed excellent agreement between the two models (Poulsen et al., 2009). This was recently confirmed by Li et al. (2013), who independently replicated and expanded this comparison to include nine compounds. Again, excellent correlation ($R^2 = 0.95$) was observed between the relative transport rates determined using the BeWo cells and transfer indices from *ex vivo* placental perfusions. Together, these studies validate the utility of the BeWo cell model as a predictor of placental transport.

Nevertheless, it is important to recognize that the aforementioned comparisons employed small molecule compounds, not nanoparticles. One cannot assume that both models will provide matching profiles of nanoparticle transfer data, but this does not mean that one model should be abandoned in favor of the other. The study of nanoparticle transport across the placenta represents a relatively unexplored area, and we need to gather more information to better understand the complexities and the possibilities regarding the interactions of nanomaterials with the placenta. Nikitina et al. have stated that focus should be placed on primary models ''at least until the mechanisms of nanotransport and nanotoxicity in human placenta are sufficiently understood and the similarity to, e.g. BeWo cells is confirmed''. In order to assess the utility of these experimental models, comparisons of nanoparticle transport across both BeWo cells and perfused placenta are necessary. Otherwise, the desired confirmation of ''similarity'' could never be determined. Such comparisons are already underway, including our recent investigation of the transplacental transfer of silica nanoparticles using both experimental models (Poulsen et al., 2015).

Both models have their place in this undertaking. Although cell lines cannot provide the same level of pharmacokinetic information as an *in vivo* study, cell culture models have played a role in high throughput screening for many years (Audus et al., 1990). They provide a rapid prediction to guide the decision-making process; otherwise, the multiplication of more time-consuming experiments could overwhelm a team's resources.

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Returning to the initial analogy, the hiker and the helicopter pilot must work together to identify and explore the most important features of a new piece of land. Both must understand and appreciate their own limitations. Proper communication will enable them to pursue their areas of interest at both an appropriate level of detail and at a reasonable pace. Given the low success rate and time-consuming nature of placental perfusions, we prioritize the investigations in our own laboratories using both experimental models. BeWo cell experiments are employed as an initial *in vitro* screening tool, followed by more detailed studies of selected nanoformulations with the *ex vivo* perfused human placenta. Such use of multiple experimental models can expand our understanding of the interactions of nanoparticles with the maternal–fetal interface at an appropriate level of detail and at a reasonable pace.

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