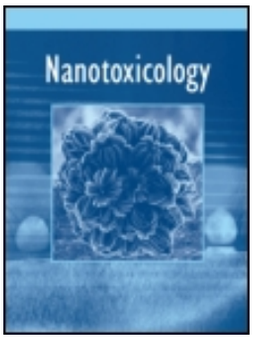

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LETTER TO THE EDITOR

# *In vitro* models of the human placental barrier – *In regione caecorum rex est luscus*

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The development of engineered nanomaterials has been on a steep rise in the last 10 years, and many of these new materials have found their way into consumer products (PEN, 2013). Given the overwhelming number of newly developed nanomaterials, the cost of rigorous toxicological assessment of all of them is estimated to be enormous (Choi et al., 2009). Therefore, resourceful testing strategies are essential to overcome the associated cost of toxicity testing while at the same time achieving the highest possible degree of safety. In this endeavor, high throughput screening tools are paramount for rapid preliminary assessment of a variety of nanomaterials. Despite being a relatively simple model of the human placental barrier, the easily maintainable choriocarcinoma derived cell line BeWo has been invaluable as a screening tool for a variety of xenobiotics (Levkovitz et al., 2013; Prouillac & Lecoeur, 2010; Saunders, 2009). Despite the fact that the cell line is malignant in origin, it has been demonstrated that the BeWo cell model has many similarities to normal trophoblast cells, which are of relevance to both toxicity and transport assessment. These similarities include placental hormone secretion (Sastry, 1996), close cell apposition and apical microvillous projections (Bode et al., 2006), and the ability to form a confluent monolayer with functional polarity (Bode et al., 2006; Cariappa et al., 2003). BeWo cells have also been shown to differentially express enzymes and transporters such as cytochrome P450 and Pgp with responses similar to trophoblasts *in vivo* (Jin & Audus, 2005; Thadani et al., 2004; Vähäkangas & Myllynen, 2006).

With the rapid development of nanotechnology there is a need for a model that can be used in preliminary toxicological screening for assessing safety of nanoparticle exposure during pregnancy. It has been estimated that a successful placental perfusion experiment is achieved every two weeks (Günday & Schneider, 2012), which is an unacceptable cost if this model alone was to be employed for nanotoxicological assessment. This model also requires large amounts of nanoparticles because of the circulation volume required and it is dependent upon the provision of placentae that are in good condition and provided in a timely manner. Using the BeWo model, areas of particular concern can rapidly be identified and subsequently tested in more sophisticated models which are less easily accessible and therefore more costly, both in terms of time and resources. For example, using the BeWo model we recently found that the toxicological profile of $Fe_3O_4$ nanoparticles (NPs) with different surface coatings resulted in a more complex dose and time-dependent response than exposure to different sizes of silica NPs (Correia Carreira et al., 2015). This finding allows us to allocate resources for further testing more efficiently.

The transport of a variety of chemicals studied both in the placental perfusion and the BeWo model have been found to be in good agreement (Correia Carreira et al., 2011; Li et al., 2013; Poulsen et al., 2009) which is a very promising result. Due to their colloidal nature, however, nanoparticles may sediment and therefore lead to more discrepancies in both models. Further work in developing and refining the BeWo model is undoubtedly required to adapt to the assessment of particulate as opposed to soluble agents. Nevertheless, using the BeWo model as a rapid screening tool proceeding *ex vivo* placental perfusion studies allows refinement of experimental conditions, such as determining appropriate concentration ranges. This enables the more scarce experimental resources such as intact perfused placentae to then be used to maximum advantage.

Placental perfusion and placental explant models are almost entirely restricted to term placenta, unless placentae from pregnancy terminations can be obtained which brings more complex ethical considerations into play). These models are therefore limited to assessing nanoparticle transport in late pregnancy but no conclusions can be drawn for the early, most sensitive stages of fetal development. The early placenta possesses multiple trophoblast layers whereas third trimester placenta bear a single trophoblast layer. Primary trophoblast cells can be isolated from human placental tissue but contamination with other cell types requires good separation and purification procedures and the formation of an intact polarized monolayer has proven difficult to achieve for transport studies (Vähäkangas & Myllynen, 2006). A multilayered trophoblast can be simulated using BeWo cells, and this model has in fact shown that nanoparticle toxicity was more pronounced in BeWo multilayers-a simple model of early placentae compared to a BeWo monolayer (Sood et al., 2011). Thanks to the flexibility of the BeWo model, it is possible to make a discovery like this which can be subsequently verified using a more sophisticated and

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hard-to-come-by model such as an early trimester placental explants (Miller et al., 2005). Issues such as sedimentation of particles can be addressed through the use of appropriate equipment to maintain particles in suspension.

By no means is the BeWo model to replace more complex models such as *ex vivo* placental perfusion or placental explants culture. No single model is going to provide us with all the answers to what the biological outcomes will be of gestational exposure to nanoparticles. Ultimately, we will need to work with a combination of models, including assessment of NP toxicity in the most appropriate *in vivo* model, to advance the field and to provide us with the answers that are needed. However, given the high cost and limited availability of such complex models on the one hand, and the overwhelming number of nanomaterials that require safety assessment on the other, alternative and less costly models are needed which can provide us with a rapid throughput to be able to test a number of variables in a short period of time under replicable conditions. As put by the Renaissance humanist Erasmus of Rotterdam: ''*In regione caecorum rex est luscus*'' (In the land of the blind, the one-eyed man is king). The ''one-eyed view'' on placental transport and toxicity we gain from the BeWo model enables us to begin to tackle the enormous task of rigorous nanoparticle safety assessment in pregnancy. This would hardly be possible if we were solely relying on the ''two-eyed view'' we may obtain from more complex models.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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