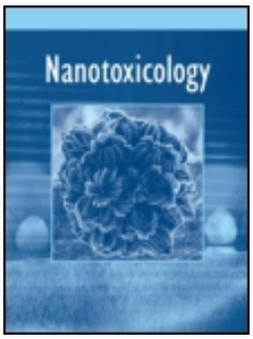

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LETTER TO THE EDITOR

Studying nanoparticle interaction with human placenta: Festina lente!

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The currently increasing awareness of an alarming lack of specific knowledge on developmental nanotoxicity significantly adds to the anyway growing anxiety about possible adverse health effects of nanomaterials. Therefore, any studies addressing nanomaterial interference with human placenta are indeed much-needed. The lessons learned about size and structure, as well as surface dependency of beneficial and toxic effects in the nano world so far (Maynard et al., 2011) suggest a nearly unlimited variability of nanomaterials with remarkably different biokinetics. This diversity has obviously been encouraging researchers to seek for high throughput nanotoxicology testing to accelerate doubtlessly overdue data collection.

Correia Carreira et al. (2015) and Poulsen et al. (2015) considered a BeWo cell monolayer-based model as a suitable *in-vitro* approach for the testing of nanoparticle (NP) transport and toxicity at the ''human placental barrier''. However, the placental barrier is known as a structural and physiological phenomenon significantly changing during pregnancy. Notably in early gestation the human placental barrier consists of two functionally interrelated trophoblast cell layers separated from fetal endothelial cells by specific extracellular matrix components, e.g. a basal membrane. The thickness of the trophoblast barrier decreases during gestation comprising of the syncytium and some discontinuously distributed cytotrophoblast cells underneath in third trimester (Huppertz, 2011). Considering the unique physiology of the placental syncytium (Huppertz & Gauster, 2011) and the structural complexity of the placental barrier *in vivo*, it appears difficult to decide which stage of pregnancy a monolayer of BeWo cells exactly represents, if any. The relevance of the developmental changes of the barrier for NP biokinetics is exemplified by a prominent difference in immunoglobulin (~10 nm particles) distribution at the feto–maternal interface between early gestation and term (Palmeira et al., 2012). Consequently, studies employing the sophisticated term placenta perfusion model (e.g. Poulsen et al., 2015), but even more studies using only a single monolayer of choriocarcinoma cells like BeWo on a crude collagen matrix (e.g. Correia Carreira et al., 2015 or Ali et al., 2013), do not explain much about nano biokinetics in early human gestation (Juch et al., 2013). Especially, the critical period of organogenesis, when severe malformations can be induced, is not represented by such experiments, an essential teratologic issue worth mentioning in the discussions.

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Furthermore, being originated from malignant invasive tumor cells, the similarity of BeWo to primary trophoblasts was shown to be significantly limited (Bilban et al., 2010). Thus, it has been regarded mandatory for each investigated pathway in BeWo cells to confirm the results in primary trophoblast cell and tissues (e.g. Knöfler et al., 1998; Orendi et al., 2011). Since the mechanisms of NP transport and toxicity particularly in the syncytium of human placenta are largely unknown, it is yet unclear and questionable if BeWo cells can serve as a physiologically plausible model in this context.

Another major concern when comparing the *in-vitro* BeWo model to a perfused placental cotyledon (Poulsen et al., 2015) is the potential sedimentation of NPs. For NPs with higher density than the culture medium (e.g. iron or gold containing materials), a considerable concentration gradient (Teeguarden et al. 2007) towards the BeWo-layer due to gravitation could obscure dose dependency assumptions of permeability. In a permanently perfused cotyledon with a pulsative administration of NPs, such gravitation phenomena would not drive the uptake at the syncytium. From this perspective, similarity in permeability between the perfusion model and the BeWo model for a certain NP might indicate a much higher uptake and transport activity in the syncytium compared to the BeWo cells. It seems necessary, though, to carefully monitor the influence of such NP typical phenomena on transport efficacy when comparing these placenta models.

Easy to handle ''high throughput'' *in-vitro* models are understandably attractive, suggesting rapid progress in this huge new field of nano biokinetics at the feto–maternal interface. Nevertheless, it might be beneficial, according to the old motto ''festina lente'' (make haste slowly), not to oversimplify the complex phenomenon ''placental barrier'' but to focus more intensively on the laborious and time consuming, but closer to placenta physiology, ''gold standard'' models like placenta perfusion (Wick et al., 2010), placental explant culture (Miller et al., 2005) or primary cell culture, 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.

References

Ali H, Kalashnikova I, White MA, Sherman M, Rytting E. 2013. Preparation, characterization, and transport of dexamethasone-loaded polymeric nanoparticles across a human placental in vitro model. Int J Pharm 454:149–57.

Bilban M, Tauber S, Haslinger P, Pollheimer J, Saleh L, Pehamberger H, et al. 2010. Trophoblast invasion: assessment of cellular models using gene expression signatures. Placenta 31:989–96.

Correia Carreira S, Walker L, Paul K, Saunders M. 2015. The toxicity, transport and uptake of nanoparticles in the in vitro BeWo b30

placental cell barrier model used within NanoTEST. Nanotoxicology 9(S1):66–78.
Huppertz B, Gauster M. 2011. Trophoblast fusion. Adv Exp Med Biol 713:81–95.
Huppertz B. 2011. Nanoparticles: barrier thickness matters. Nat Nanotechnol 6:758–9.
Juch H, Nikitina L, Debbage P, Dohr G, Gauster M. 2013. Nanomaterial interference with early human placenta: Sophisticated matter meets sophisticated tissues. Reprod Toxicol 41:73–9.
Knöfler M, Stenzel M, Husslein P. 1998. Shedding of tumour necrosis factor receptors from purified villous term trophoblasts and cytotrophoblastic BeWo cells. Hum Reprod 13:2308–16.
Maynard AD, Warheit DB, Philbert MA. 2011. The new toxicology of sophisticated materials: nanotoxicology and beyond. Toxicol Sci 120: 109–29.
Miller RK, Genbacev O, Turner MA, Aplin JD, Caniggia I, Huppertz B. 2005. Human placental explants in culture: approaches and assessments. Placenta 26:439–48.
Orendi K, Kivity V, Sammar M, Grimpel Y, Gonen R, Meiri H, et al. 2011. Placental and trophoblastic in vitro models to study preventive and therapeutic agents for preeclampsia. Placenta 32: S49–54.
Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. 2012. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol 2012:985646:1–13.
Poulsen MS, Mose T, Maroun LL, Mathiesen L, Knudsen LE, Rytting E. 2015. Kinetics of silica nanoparticles in the human placenta. Nanotoxicology 9(S1):79–86.
Teeguarden JG, Hinderliter PM, Orr G, Thrall BD, Pounds JG. 2007. Particokinetics in vitro: dosimetry considerations for in vitro nanoparticle toxicity assessments. Toxicol Sci 95: 300–12.
Wick P, Malek A, Manser P, Meili D, Maeder-Althaus X, Diener L, et al. 2010. Barrier capacity of human placenta for nanosized materials. Environ Health Perspect 118:432–6.