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An international network (PlaNet) to evaluate a human placental testing platform for chemicals safety testing in pregnancy

Paul Brownbill[a,b,*], Igor Chernyavsky[c], Barbara Bottalico[d], Gernot Desoye[e], Stefan Hansson[d], Gerry Kenna[f], Lisbeth E. Knudsen[g], Udo R. Markert[h], Nicola Powles-Glover[i], Henning Schneider[j], Lopa Leach[k]

[a] *Maternal and Fetal Health Research Centre, Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK*
[b] *Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK*
[c] *School of Mathematics, University of Manchester, Manchester, UK*
[d] *Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Lund University, Lund, Sweden,*
[e] *Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria*
[f] *Safer Medicines Trust, Macclesfield, UK*
[g] *Department of Public Health, Faculty Of Health Sciences, University of Copenhagen, Denmark*
[h] *Placenta-Labor Laboratory, Department of Obstetrics, Friedrich Schiller University, D-07740, Jena, Germany*
[i] *Reproductive, Development and Paediatric Centre of Excellence, AstraZeneca, Mereside, Alderley Park, Alderley Edge SK10 4TG, UK*
[j] *Department of Obstetrics and Gynecology, Inselspital, University of Bern, Switzerland*
[k] *Molecular Cell Biology & Development, School of Life Sciences, Faculty of Medicine & Health Sciences, University of Nottingham, UK*

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ABSTRACT

The human placenta is a critical life-support system that nourishes and protects a rapidly growing fetus; a unique organ, species specific in structure and function. We consider the pressing challenge of providing additional advice on the safety of prescription medicines and environmental exposures in pregnancy and how *ex vivo* and *in vitro* human placental models might be advanced to reproducible human placental test systems (HPTSs), refining a weight of evidence to the guidance given around compound risk assessment during pregnancy. The placental pharmacokinetics of xenobiotic transfer, dysregulated placental function in pregnancy-related pathologies and influx/efflux transporter polymorphisms are a few caveats that could be addressed by HPTSs, not the specific focus of current mammalian reproductive toxicology systems. An international consortium, "PlaNet", will bridge academia, industry and regulators to consider screen ability and standardisation issues surrounding these models, with proven reproducibility for introduction into industrial and clinical practice.

Abbreviations: PlaNet, placentology network; HPTSs, human placental test systems; FDA, Food and Drug Administration; EMA, European Medicines Agency; PLLR, pregnancy and lactation labelling rule; IVS, intervillous space; HUVEC, human umbilical vein endothelial cell; NET, norepinephrine transporter; EMT, extra-neural monoamine transporter; VMAT2, vesicular monoamine transporter 2; NOAEL, no observed adverse effect level; LOAEL, lowest observable adverse effect level; DART, development and reproductive toxicology testing.

* Corresponding author at: Maternal and Fetal Health Research Centre, Institute of Human Development, University of Manchester, St. Mary's Hospital, Oxford Road, Manchester M13 9WL, UK.

E-mail addresses: paul.brownbill@manchester.ac.uk (P. Brownbill), igor.chernyavsky@manchester.ac.uk (I. Chernyavsky), barbarabottalico28@gmail.com (B. Bottalico), gernot.desoye@medunigraz.at (G. Desoye), stefan.hansson@med.lu.se (S. Hansson), gerry@safermedicines.org (G. Kenna), liek@sund.ku.dk (L.E. Knudsen), udo.markert@med.uni-jena.de (U.R. Markert), Nicola.PowlesGlover@astrazeneca.com (N. Powles-Glover), henning.schneider@hispeed.ch (H. Schneider), Lopa.Leach@nottingham.ac.uk (L. Leach).

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1. Introduction

The human placenta is a critical life-support system that nourishes and protects a rapidly growing fetus. The structure and function of the human placenta is unique [1]; although rats and rabbits are valid models in the evaluation of potential teratogens, interpretation of their transplacental xenobiotic transfer data is precarious. The fetus is potentially vulnerable to xenobiotics that cross the placental barrier, which either cause direct damage to the fetus, or indirectly affect embryo development by interfering with normal placental function.

Even subtle alterations of the fetal-placental environment may have a lasting effect on health in later life and so create a significant economic burden on healthcare economies. Understanding differences in how xenobiotics are handled by the human placental barrier in the diseased state, compared to normal pregnancy, is also a pressing concern (see below). Hence, there is a need to evaluate evidence for differences and consider how HPTSs might be adapted to meet future niche study demands. The uteroplacental compartmentalisation of biopharmaceuticals is most likely different in humans, since such compounds are often handled by receptor-mediated endocytosis that differs in other mammals; and the relevance of these medicines will expand in the future [2,3]. Below, we outline several HPTSs that could be advanced to standardised applications for use in toxicology testing.

2. Consideration of human placental test systems (HPTSs)

2.1. Added value to mammalian testing

Currently zebrafish larvae and stem cell models are becoming accepted worldwide as a pre-screening tool for embryofetal developmental endpoints. These models are beginning to complement mammalian reproductive toxicology testing, conducted much later in the drug development lifetime [4–6]. However, the zebrafish and stem cells lack a placenta. In order to add a further weight of evidence to the mammalian regulatory studies, there are plans to develop human placental assays. A human placental testing platform may help fill this technology gap (see Fig. 1). The human placenta is a readily available, ethically unproblematic human tissue that could be used to assess placental effects and human transplacental transfer, subject to conforming to national and institutional guidelines and the standards set by the Declaration of Helsinki [7]. This declaration guides physicians and researchers in the ethical principles of handling human subjects, human tissue and associated data, to safeguard the health and interests of people. Professionals must act primarily in the interests of patients. Whilst the declaration accepts that experimentation on humans is an inevitable part in the advancement of medicine, it upholds the interests of the patient as a precedent above advancements of science and society. It defines the usefulness of medical research in the development of prophylactic, diagnostic and therapeutics, as well as in providing an understanding of disease aetiology. Consent must be achieved, but only if the participant is able to make an informed choice without coercion; and where processes are also subject to local statute.

Careful thought is needed to address many caveats in the introduction of a new human testing program. For instance, the responses to toxins are sometimes dependent on genetic predispositions affected by ethnic diversity and environmental conditions [8–10]. Since ethnic make-up and the environment that local populations are exposed to vary enormously within and between nations, this will affect the cohort demographics of the local obstetric clinic and therefore the recruits to associated research centres where the placentas are used. It is unknown how such uncontrolled circumstances might influence variability of placental function, so research development into the utilisation of human placental tissue needs a study design inclusive of a much wider global diversity. Thus, the complexity and multi-faceted nature of toxicological testing in the context of regulatory procedures and industrial practices would require a scale of expertise and cooperation beyond a few national research centres for the evaluation of risk where human placentas are being evaluated. This paper considers the establishment of an international partnership amongst academia, the pharmaceutical industry, standardisation institutes, and the regulators, to (i) review our understanding of human placental transfer processes of xenobiotics; (ii) consider the current state-of-the art in human placental models, emerging bio-physical sensing technology and mathematical modelling; (iii) consider short-term scientific missions between academia, industry and regulators, trialling pilot studies, harmonising practices, writing standardised protocols and training a global network of laboratories in best practice; and (iv) to present outcomes of selected human placental test systems (Fig. 1).

2.2. International placentology network

A network called “PlaNet” (placentology network) is being formed, bringing under one global safety umbrella different facets of chemical effects on fetal survival, growth, function and development, building a critical mass of international cutting-edge expertise in experimental human placental test systems (HPTSs), pharmacology, toxicology, drug delivery and mathematical modelling. This umbrella will additionally cover the global education and training in chemical safety testing with human placenta-based techniques. PlaNet aims to engage academics with the regulatory authorities, reproductive toxicology societies and the pharmaceutical and biotechnology industries, to steer the HPTSs and associated modelling approaches towards standard operating procedures, connected to meaningful screening assays, recognised by the regulators for routine compound testing. As a part of these efforts, the proposed network will also consider innovative methods towards reducing the number of animals used as drug safety models, while improving the reliability of the data.

3. Relevance and timeliness

Standardised HPTSs would provide species relevant data and enable a consideration of placental functional and transfer effects of xenobiotics. They would deliver additional evidence to complement rat and rabbit reproductive toxicology data and newly emergent zebrafish larvae and stem cell functional data used in pharmaceutical testing. With this evidence, medicines labelling could be written on a firmer basis for the informed benefit of obstetricians and patients. Proposed changes in OECD guidelines will soon necessitate a consideration of manufacturers to engage in animal and *in vitro* testing of chemicals. Standardised HPTSs may offer a cost effective means of providing data to assist in safety data sheet writing by the chemical industry.

3.1. Reproductive toxicology testing in the pharmaceutical industry

Reproductive toxicity refers to the adverse effects of a substance on any aspect of the reproductive cycle. Due to the complexity of the mammalian reproductive cycle, it is hard to model the whole cycle in a single *in vitro* system in order to detect chemical effects on mammalian reproduction [11]. Development and reproductive toxicology testing (DART) studies in rats and rabbits form the main basis for regulatory assessment of the potential effects of pharmaceuticals on the developing fetus. Current approaches assessing the