Preterm piglets as a translational model for premature babies: focus on hepatic drug metabolism

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INTRODUCTION

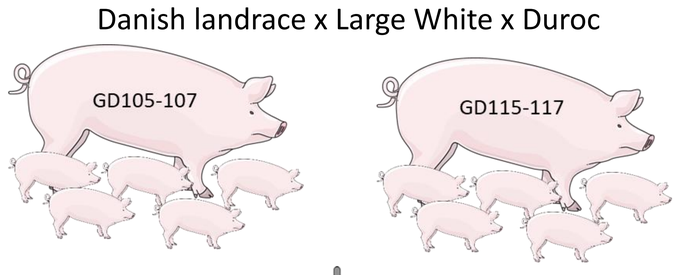
Children and especially (premature) neonates are the **most vulnerable group** in the human population with regard to the use of medicinal products. Due to the associated risks and ethical concerns, studies in juvenile animals may be warranted for safety assessment of drugs in development. In this study, we investigated the **preterm and term piglet** as a translational model for preterm and term infants. More specifically, the early Phase I biotransformation capacity was investigated focusing on hepatic **CYP3A activity**.

METHODS

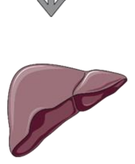
- Birth: Preterm (Gestational day (GD)105-107, N=38) & Term (GD115-117, N=56)
- Age at euthanasia: (Postnatal) Day 0, 5, 11, 19 & 26
- Two technical replicates, four biological replicates, CYP3A baculosomes as positive control

Danish landrace x Large White x Duroc

Piglets delivered by C-section

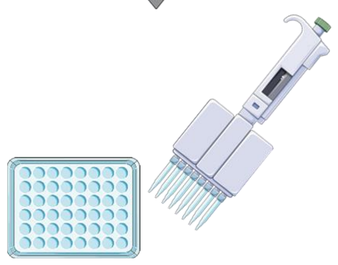


Liver samples snap frozen, stored at -80°C

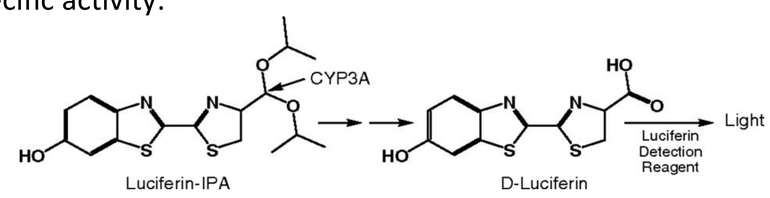


Isolation **liver microsomes** by different homogenisation, centrifugation & ultracentrifugation steps

Determination protein concentration: **BCA assay**



Determination CYP3A4-specific activity: **Luciferin-IPA assay**



RESULTS AND DISCUSSION

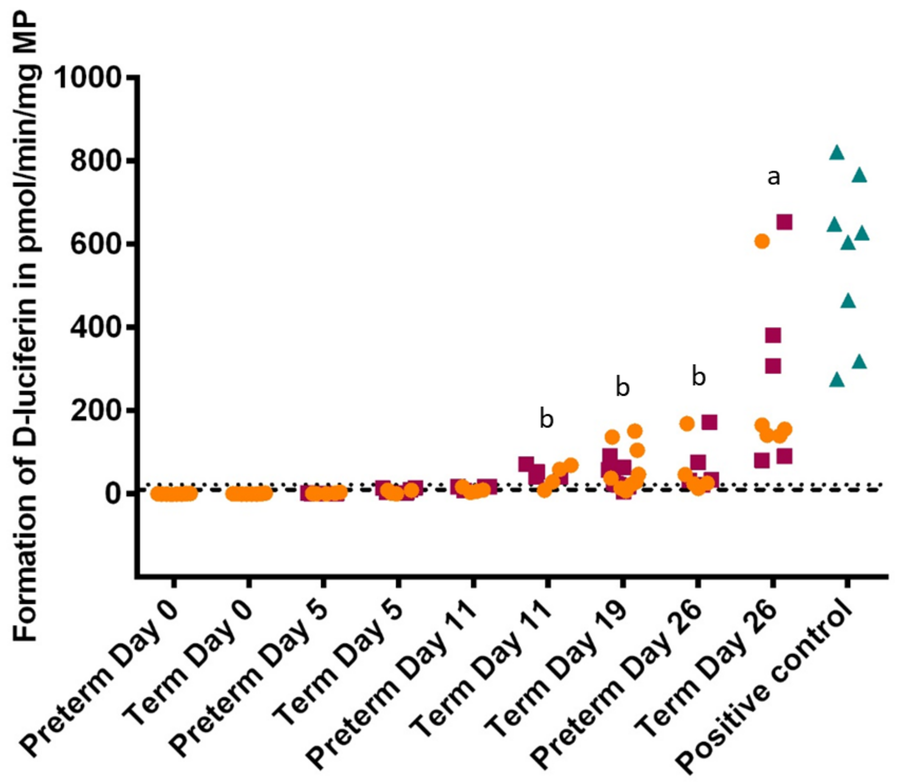


Figure 1: Formation of D-Luciferin in pmol/min/mg microsomal protein (MP). The mean value of 2 technical replicates for each animal is represented by a purple cube (female), orange dot (male) or blue triangle (positive control). Upper (dotted) and lower (dashed) horizontal lines represent the LLOQ and LLOD, respectively. Different letters indicate significant ($p<0,05$) differences between the age groups.

- CYP3A activity was detectable, but under the LLOQ for preterm and term Day 0, 5 and preterm Day 11 samples. (Only values above LLOQ were used for statistical analysis)
- There was no significant difference in CYP3A activity between term Day 11 and term Day 19 ($p=0.812$) and term Day 19 and preterm Day 26 ($p=0.799$)
- A significant difference was observed between term Day 26 on the one hand and term Day 11 ($p=0.0008$), term Day 19 ($p=0.0007$) and preterm Day 26 ($p=0.0145$) on the other hand

CONCLUSIONS AND PERSPECTIVES

- **Hepatic CYP3A activity** is detectable but **under the LLOQ** for the youngest age groups (preterm and term Day 0 & 5, preterm Day 11) and **increases** with age in other age groups
- **Gestational age** rather than postnatal age affects development of CYP3A activity
- These age groups will be further investigated for **other biotransformation enzymes** in order to further characterise the piglet as a translational model for paediatrics

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