The neonatal and juvenile Göttingen Minipig: a useful model for paediatric drug development

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INTRODUCTION

• Dose precision in neonates, infants and toddlers is challenging

• Paediatric animal models can be very valuable

• For safety assessment and disease conditions

• In our RI: neonatal and juvenile Göttingen Minipigs
OBJECTIVES

Neonatal and juvenile Göttingen Minipigs for:

• Small molecule drugs

• Single Stranded Oligonucleotides (SSOs)

• Disease models (e.g. perinatal asphyxia)
MATERIAL & METHODS

• Göttingen Minipigs

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>84-86 days of gestation</td>
<td>n = 4</td>
</tr>
<tr>
<td>108 days of gestation</td>
<td>n = 4</td>
</tr>
<tr>
<td>Day 1</td>
<td>n = 4</td>
</tr>
<tr>
<td>Day 3</td>
<td>n = 4</td>
</tr>
<tr>
<td>Day 7</td>
<td>n = 4</td>
</tr>
<tr>
<td>Day 28</td>
<td>n = 5</td>
</tr>
<tr>
<td>Adult</td>
<td>n = 5</td>
</tr>
</tbody>
</table>

• Morphometry (pH and length GI, organ weights), drug metabolism (Phase I and II – activity and abundance), PBPK, endo- and exonucleases (expression and activity), clin obs, clin chem, asphyxia model +/- cooling therapy
RESULTS – Morphometry

From PND1 to PND28:

- Gastric pH ↓↓
- Relative organ weights ↑ 1st week of life, then ↓ up to PND28
- Fast ↑ in absolute organ weights (continues up to 3-4 months)
- Linear ↑ in body weight (continues up to 5 months)

PBPK model
RESULTS – Drug metabolism

**FAST:** CYP1A2 and CYP2D6

- CYP1A2
  - Day 28-Adult: $p > 0.0025$

- CYP2D6
  - Day 28-Adult: $p > 0.0025$

**SLOW:** CYP2C9 and CYP3A4

- CYP2C9
  - Day 28-Adult: $p < 0.0025$

- CYP3A4
  - Day 28-Adult: $p < 0.0025$

HLM: human liver microsomes

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*In vitro Phase I- and Phase II-Drug Metabolism in The Liver of Juvenile and Adult Göttingen Minipigs*

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RESULTS - SSOs

The Minipig is a Suitable Non-Rodent Model in the Safety Assessment of Single Stranded Oligonucleotides

Annamaria Braendli-Baiocco,¹ ¹¹ Matthias Festag,² Kamille Dumong Erichsen,¹ Robert Persson,² Michael J. Mihatsch,³ Niels Fisker,¹ Juergen Funk,² Susanne Mohr,¹ Rainer Constien,⁶ Corinne Ploix,¹ Kevin Brady,¹ Marco Berrera,¹ Bernd Altmann,¹ Barbara Lenz,¹ Mudher Albassam,⁶ Georg Schmitt,¹ Thomas Weiser,¹ Franz Schuler,¹ Thomas Singer,¹ and Yann Tessier¹

No overt toxicity

Gene expression profiling of key nucleases in the juvenile Göttingen minipig

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https://doi.org/10.1016/j.reprotox.2019.07.058
Pharmacokinetics of dexmedetomidine combined with therapeutic hypothermia in a piglet asphyxia model

- Effect of cooling therapy
- PK of midazolam, phenobarbital, topiramate and fentanyl

Sangild et al. J ANIM SCI 2013, 91:4713-4729
CONCLUSION

• Drug metabolism of small molecule drugs & gastrointestinal parameters in neonatal and juvenile Göttingen Minipigs = paediatric population

• Also a valuable model for new modalities such as SSOs

• Opportunities for assessment of covariates that cannot be addressed in a clinical setting
ACKNOWLEDGMENTS
The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to EPTRI or the EC.