

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

Age groups	Number of animals	
	Female	Male

84-86 days of gestation	n = 4	n = 4
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108 days of gestation	n = 4	n = 4
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Day 1	n = 4	n = 4
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Day 3	n = 4	n = 4
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Day 7	n = 4	n = 5
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Day 28	n = 5	n = 5
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Adult	n = 5	n = 4
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- 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




J Pharmacokinet Pharmacodyn (2016) 43:179–190
DOI 10.1007/s10928-015-9463-8



From PND1 to PND28:

ORIGINAL PAPER

Organ data from the developing Göttingen minipig: first steps towards a juvenile PBPK model

Els Van Peer¹  • Noel Downes² • Christophe Casteleyn¹ • Chris Van Ginneken¹ • Arie Weeren³ • Steven Van Cruchten¹

- 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)

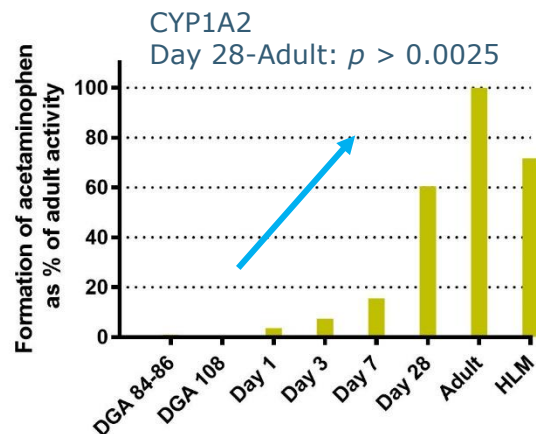
PBPK model



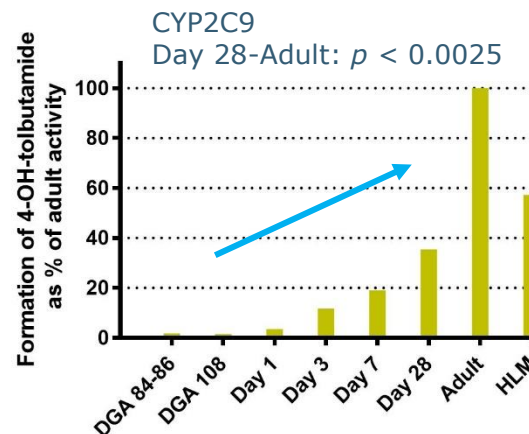
RESULTS – Drug metabolism



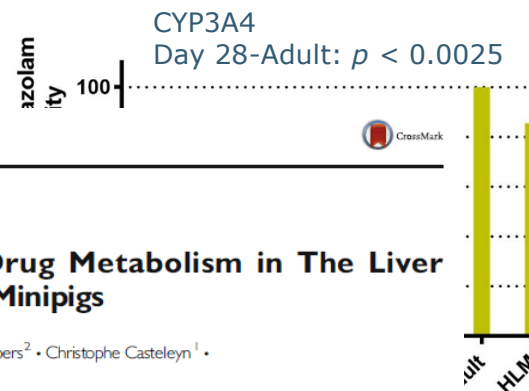
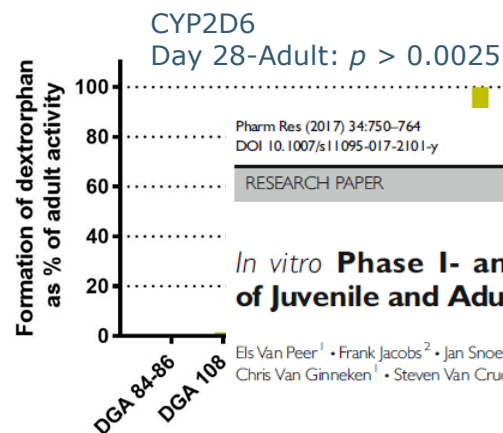
FAST: CYP1A2 and CYP2D6



SLOW: CYP2C9 and CYP3A4



HLM: human liver microsomes



Pharm Res (2017) 34:750–764
DOI 10.1007/s11095-017-2101-y

RESEARCH PAPER

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,^{*,1,2} Matthias Festag,^{*,1} Kamille Dumong Erichsen,[†] Robert Persson,[†] Michael J. Mihatsch,[‡] Niels Fisker,[†] Juergen Funk,^{*} Susanne Mohr,^{*} Rainer Constien,[§] Corinne Ploix,^{*} Kevin Brady,^{*} Marco Berrera,^{*} Bernd Altmann,^{*} Barbara Lenz,^{*} Mudher Albassam,[¶] Georg Schmitt,^{*} Thomas Weiser,^{*} Franz Schuler,^{*} Thomas Singer,^{*} and Yann Tessier[†]



No overt toxicity

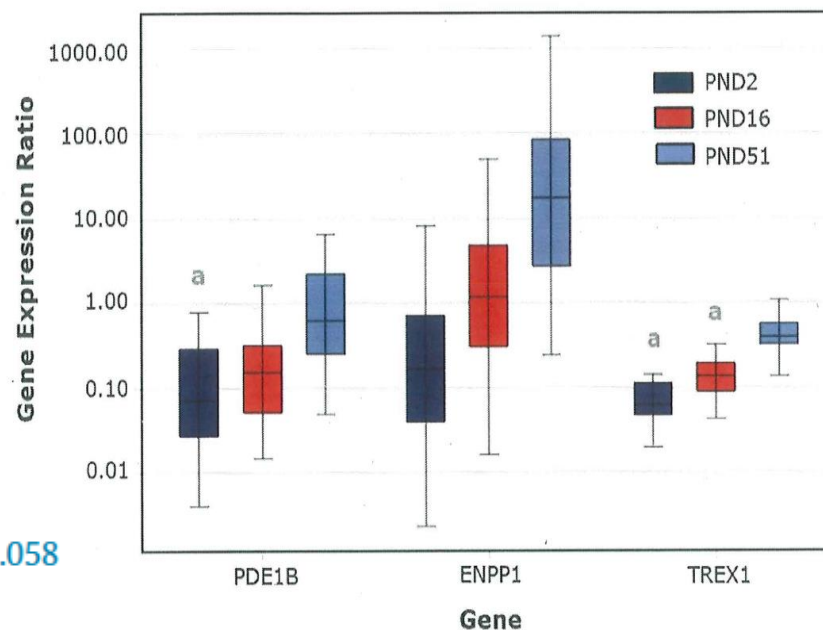
Gene expression profiling of key nucleases in the juvenile Göttingen minipig

Allan Paulo Valenzuela^{1,*}, Laura Buysens¹, Chloé Bars¹, Miriam Ayuso¹, Chris Van Ginneken¹, Neil Parrott², Yann Tessier², Georg Schmitt², Paul Barrow², Steven Van Cruchten¹

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<https://doi.org/10.1016/j.reprotox.2019.07.058>



Neonatal asphyxia model



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ACTA ANAESTHESIOLOGICA SCANDINAVICA

doi: 10.1111/aas.12318

Pharmacokinetics of dexmedetomidine combined with therapeutic hypothermia in a piglet asphyxia model

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



PBPK model



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



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GÖTTINGEN MINIPIGS

janssen
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OF Johnson & Johnson


**GHENT
UNIVERSITY**

Roche


sequani
NON CLINICAL
great people, great work, real results

KU LEUVEN

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