ELLEGAARD
GÖTTINGEN MINIPIGS

Welcome to the webinar:

Drug metabolism in Göttingen Minipigs: Critical information for species selection in drug safety testing

24 February 2021

Guest speaker: Steven Van Cruchten | University of Antwerp, Belgium

- Many have signed up for this webinar from around the world and therefore all attendees are muted to avoid background noises, delays in sound, echoes etc.
- Please ask your questions in the questions/chat section and we will follow up in the Q&A session following the presentation.
- We encourage everyone to complete the survey after the webinar, so we can continue planning relevant, educational and insightful webinars.
- Presentation slides and a recording of the webinar will be shared within 1-2 days via email.
- Certificates of attendance are available upon request. Please email events@minipigs.dk

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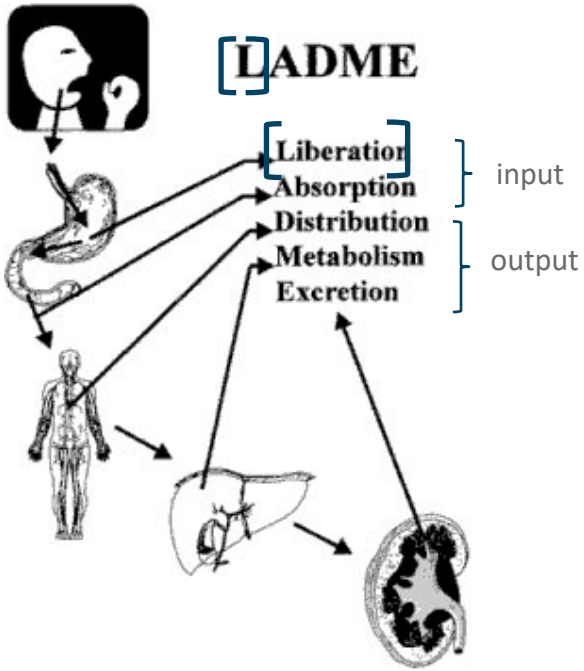
Outline

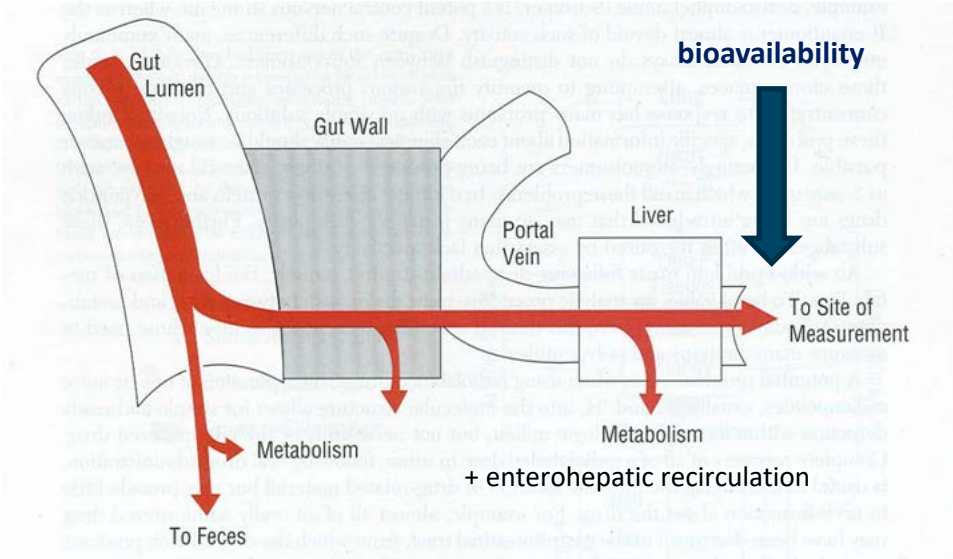
- Importance of AD**M**E – in vitro drug metabolism assays in species selection
- Metabolism of SMEs in adult population
- Metabolism of SMEs in paediatric population
  - Metabolism of SMEs in paediatric disease models
- Metabolism of ASOs in paediatric population

ADME - PK: some basics

Pharmacokinetics (PK)

Relationships between the dosage regimen and the profile of the drug concentration in blood and tissues over time

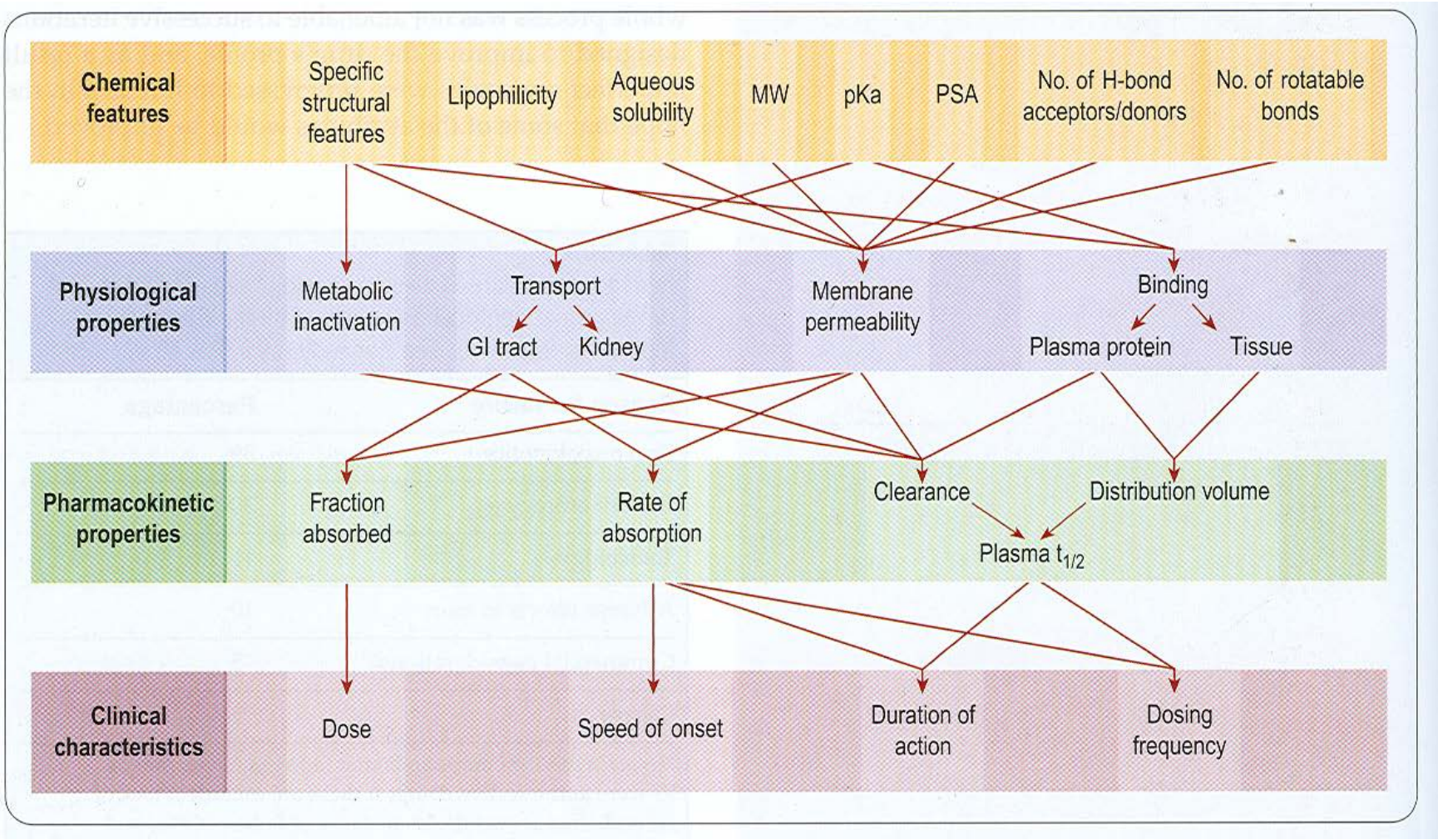




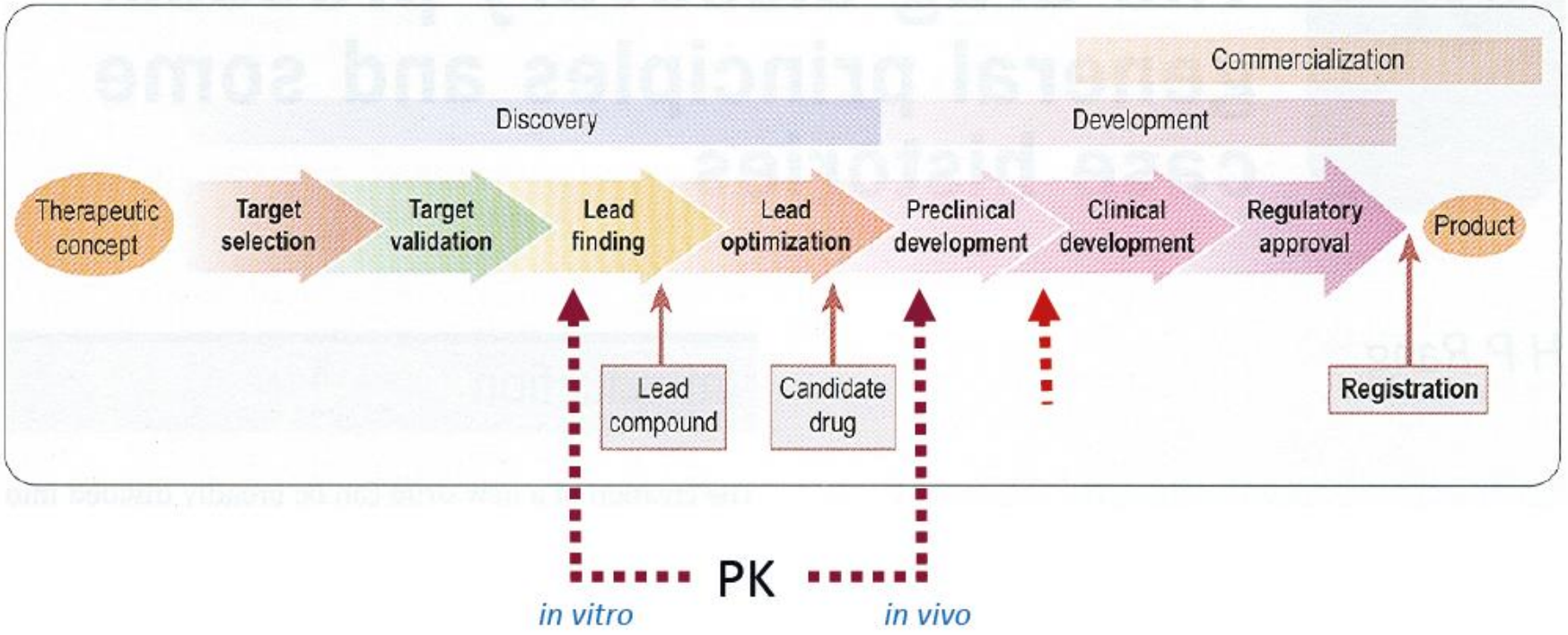
Pharmacodynamics (PD)

Relationships between the drug concentration-time profile and therapeutic and adverse effects

Drug properties & PK characteristics



Positioning of PK in drug discovery/development



Importance of early PK evaluation

Early pharmacokinetic evaluation is pivotal

- *Efficacy*
- *Safety*
- *Convenient use*

Lead optimization

Lead identification

Reasons for failure in clinical development. (Data for 198 development compounds analysed by the Centre for Medicines Research; see Kennedy (1997))

Reason for failure	Percentage
Pharmacokinetics	39
Lack of efficacy	30
Toxicology	11
Adverse effects in man	10
Commercial considerations	5
Others	5

Note: Of the 198 compounds that failed in development, 77 were anti-infective drugs; if these are excluded, lack of clinical efficacy was the main cause of failure (49%), and pharmacokinetic failures were less common (7%).

" fail fast - fail cheap "

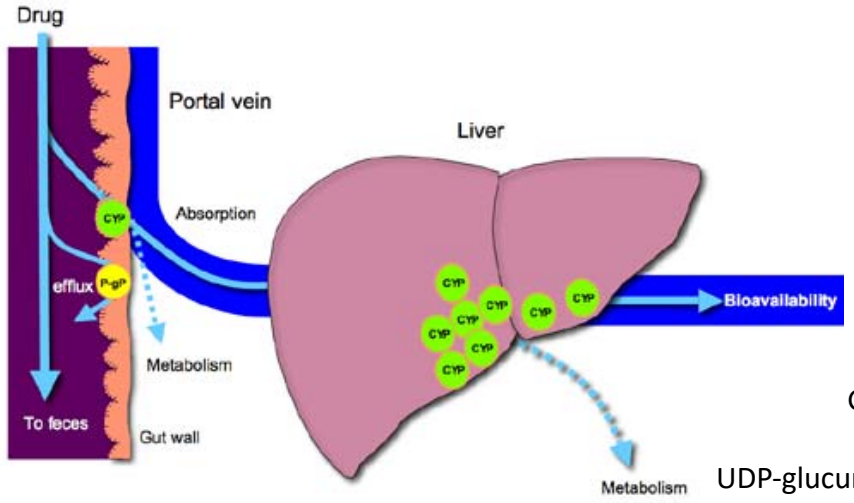
ADME – drug metabolism

prodrugs → **drugs** → **metabolites**

microsomal — **Biotransformation** — *cytosolic*

Phase-I

CYP_{450}

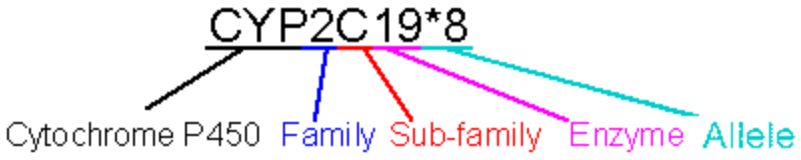


Phase-II

Conjugating enzymes

Glutathione S-transferase (GST)
N-acetyl transferase (NAT)
UDP-glucuronosyl transferase (UGT) => microsomes

CYP450 enzymes



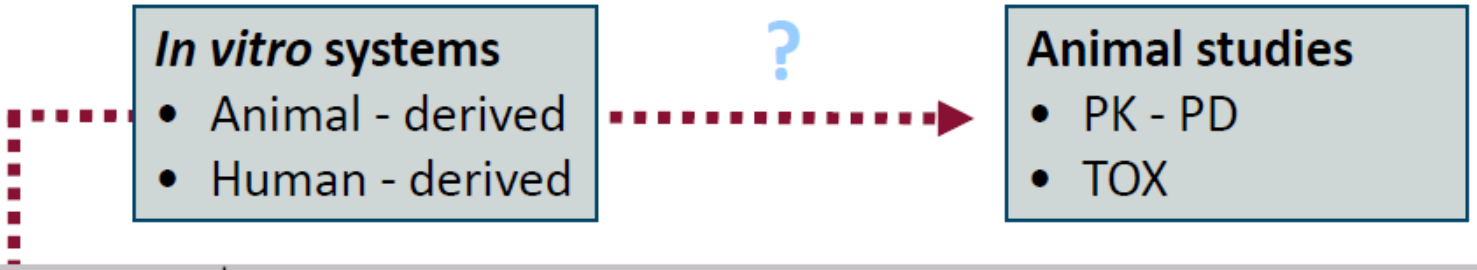
Haem-containing mono-oxygenase enzymes that play an important role in the oxidative metabolism of endogenous substances, natural products and xenobiotics

CYP450	Relative amount in liver (%)	Selective inhibitors	Characteristics
1A2	~10	Furafylline	Inducible #
2A6	~10		Polymorphic *
2B6	~1	Orphenadrine	
2C8	<1	Quercetin	
2C9	~20	Sulfaphenazole	Polymorphic *
2C19	~5		Polymorphic *
2D6	~5	Quinidine	Polymorphic *
2E1	~10	Pyridine	Inducible #
3A4	~30	Azole antimycotics	Inducible #
>55 CYP-genes sequences in human genome // four human CYP families (CYP1-4)			

* **Inter-individual variation**

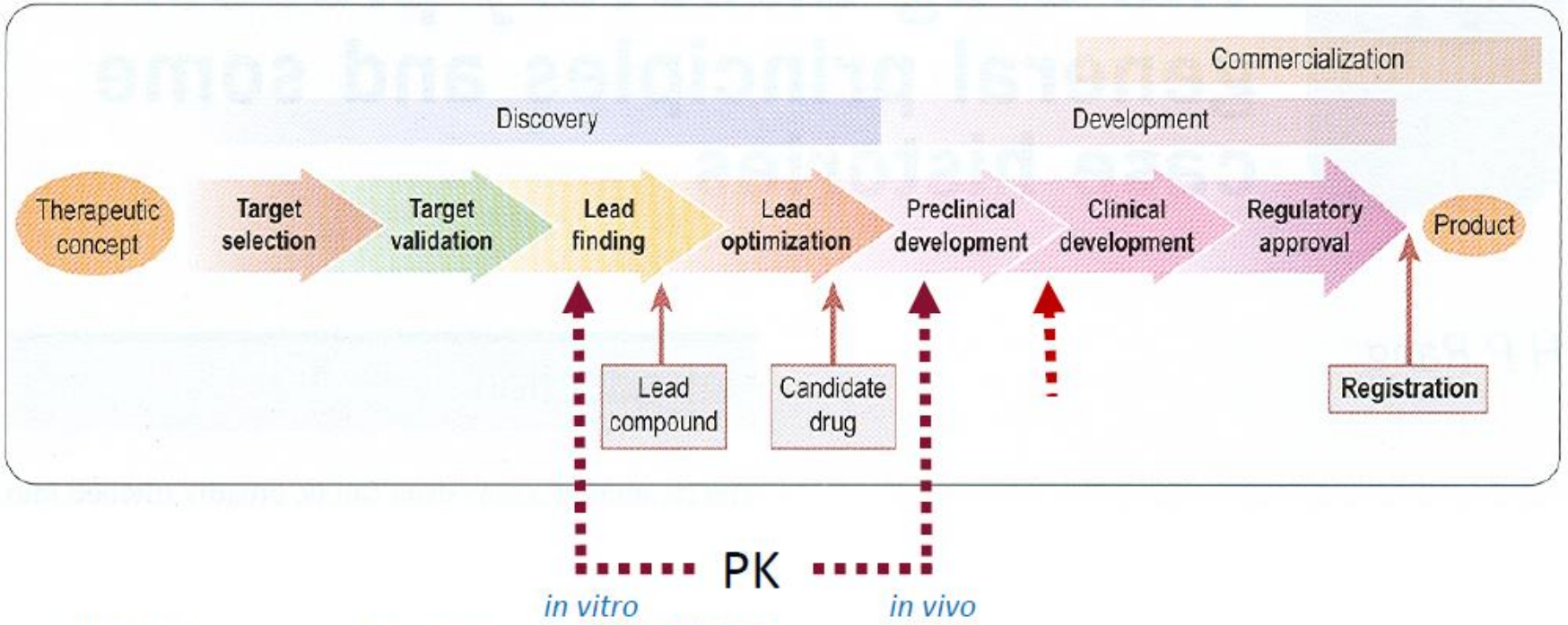
\# **Drug interactions**

In vitro drug metabolism assays



Test system	Basic characteristics
Liver microsomes (S9)	fractioned from subcellular organelles by ultracentrifugation --> smooth endoplasmic reticulum contains full complement of P450-enzymes phase-II: addition of appropriate cofactors (conjugation enzymes)
cDNA CYP's	individual enzymes produced in ER of host cell by gene expression (bacteria, yeast, mammalian cell, ..) most useful tool for HTS P450 screening (MS-detection, fluorescence)
Permanent cell lines	poor and variable expression level - lack the complement of relevant enzymes
Primary hepatocytes	contain the full complement of phase-I and phase-II enzymes and co-factors
	induction of drug-metabolizing enzymes and hepatotoxicity can be assessed
	higher metabolizing capacity --> qualitative metabolite profiling
Live slices	resemble most closely the *in vivo* situation --> connection between individual cells

In vitro drug metabolism assays: nonrodent species



Cellular /tissue
- Hepatocytes
- Liver slices

✓ ✓

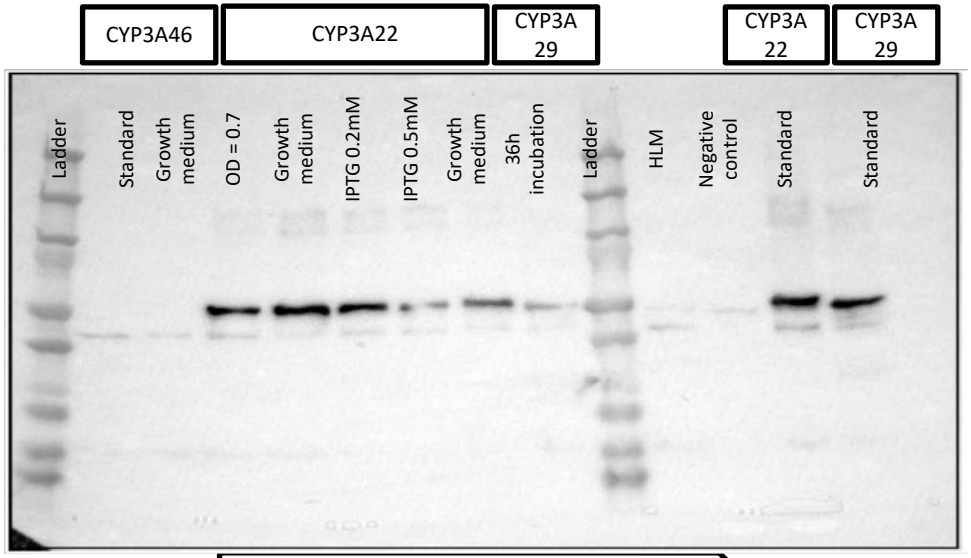
Subcellular
- microsomes
- S9 fraction

Recombinant

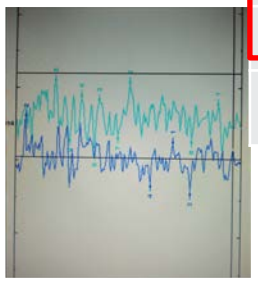
✓ ✓ ✓

✓ ✓ ✓

Göttingen Minipig rCYP3A isoforms: ongoing activities



CYP	Condition	pmol/min/mg MP	LLOD/ LLOQ
46	Standard	1,36	<LLOD
46	Warm TB	2,36	<LLOD
22	OD = 0.7	34,4	>LLOQ
22	New TB	27,8	>LLOQ
29	36h incub	-0,35	<LLOD



Western Blot

Spectrophotometry Luminescence assay (CYP3A4-like)

Expression/Activity?

In practice:

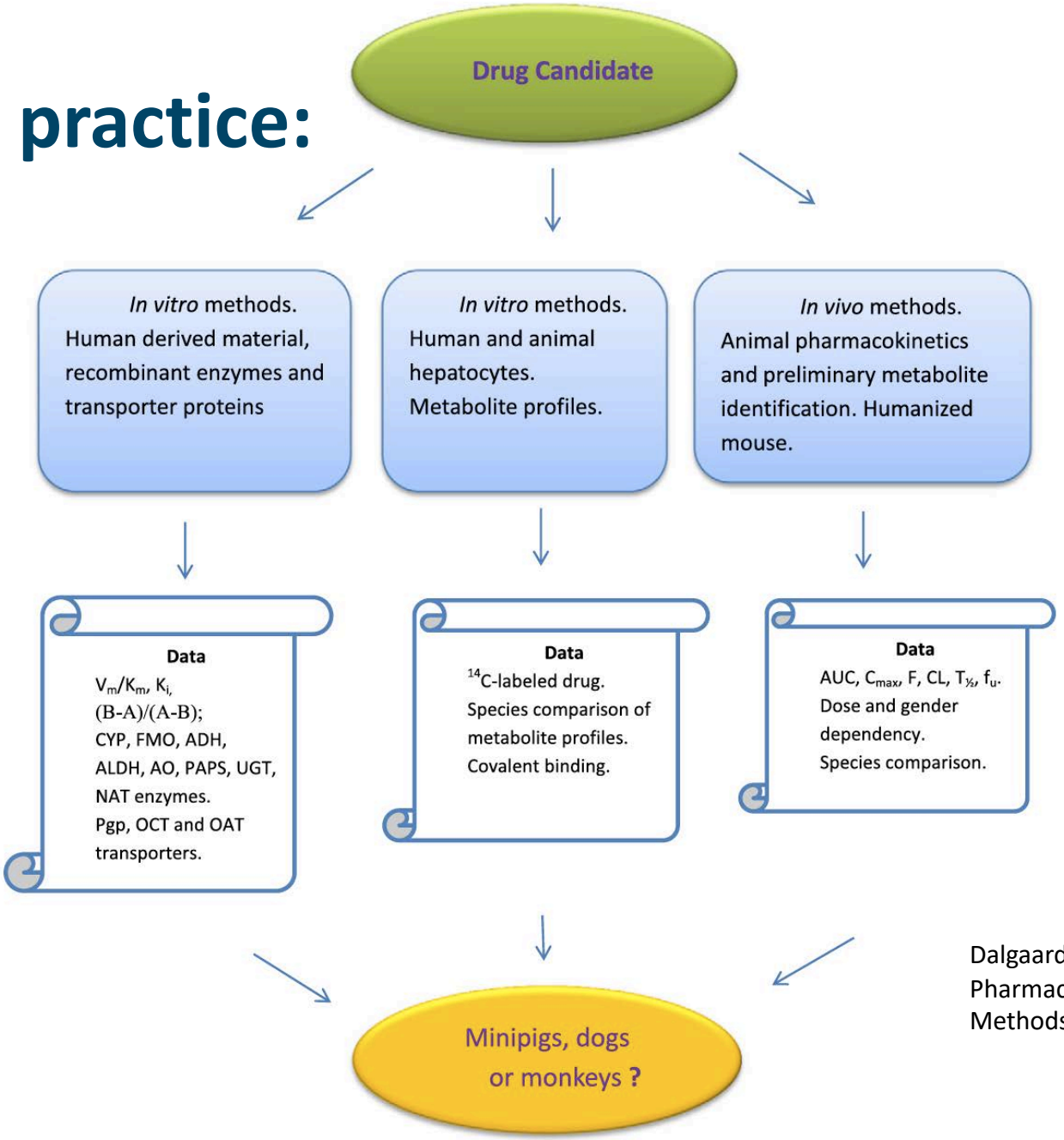


Fig. 1. ADME methods and data produced early in the development phase of a new drug.

Dalgaard et al. Journal of Pharmacological and Toxicological Methods. 2015, 74:80-92.

Conclusion in vitro drug metabolism: species comparison - selection

- Several in vitro drug metabolism assays for man, dog, minipig and nonhuman primates

- Recombinant enzymes for Göttingen Minipig still lacking, but under development

- Despite the presence of several in vitro drug metabolism assays for Göttingen Minipig, most companies do not include this nonrodent species in their testing battery

DMEs in adult population: species comparison

Hepatic CYPs – species comparison

Table 1
Total liver content of CYP enzymes in humans, monkeys, pigs and dogs.

Species	Total liver content of CYP (nmol/mg protein)	References
Humans	0.29 ± 0.06 (n = 12) 0.307 ± 0.16 (n = 18)	Stevens et al. (1993) and Shimada et al. (1997)
Rhesus monkeys	0.95 ± 0.08 (n = 6)	Stevens et al. (1993)
Cynomolgus monkeys	1.03 ± 0.11 (n = 5)	Shimada et al. (1997)
Minipigs	0.81 ± 0.15 (n = 9)	Nebbia et al. (2003)
Pigs	0.22 ± 0.12 (n = 3) 0.46 ± 0.07 (n = 12)	Shimada et al. (1997), Myers et al. (2001) and M T Skaanild and Friis (1999)
Dogs	0.39 ± 0.04 (n = 6)	Shimada et al. (1997)

Dalgaard et al. Journal of Pharmacological and Toxicological Methods. 2015, 74:80-92.

Table 3

Comparison between human and pig or minipig CYP enzymes.

CYP1A2	The EROD activity of sexually-mature minipigs is 2–4 times higher than in males (Skaanild & Friis, 1999); (as opposed to humans); pig and human CYP1A very similar (Bogaards et al., 2000; Madden et al., 1998; Nebbia et al., 2003; Shimada et al., 1994; Skaanild & Friis, 1999). Induction by the same inducers across species (Behnia et al., 2000; Desille et al., 1999; Lu & Li, 2001; Monshouwer et al., 1998).
CYP2A, CYP2B	Major problems in extrapolations (Bogaards et al., 2000; Gillberg et al., 2006; Myers et al., 2001; Shimada et al., 1994; Skaanild & Friis, 1999).
CYP2C	Carries both 2C9 and 2C19 characteristics (share substrates) (Anzenbacher et al., 1998; Myers et al., 2001; Skaanild & Friis, 2007).
CYP2D	More caution needed: some CYP2D6 substrates are also substrates in pigs, but pig 2B seems to be responsible for this (Bogaards et al., 2000; Skaanild & Friis, 2002).
CYP2E1	High similarity between pig/minipig and human, some caution in extrapolation (Bogaards et al., 2000; Skaanild & Friis, 1999).
CYP3A	Similar to human and more than one CYP3A. Inducible by rifampin, but not by dexamethasone (Hosagrahara et al., 1999; Bogaards et al., 2000; Desille et al., 1999; Madden et al., 1998; Skaanild & Friis, 1999).

Dalgaard et al. Journal of Pharmacological and Toxicological Methods. 2015, 74:80-92.

CYP activity in man and nonrodents

Table 2
CYP activity ratios in monkeys, minipigs and dogs relative to humans.

		Turpeinen et al. 2007			Sharer et al. 1995		
Substrate	Human CYP	Cynomolgus monkey	Göttingen minipig	Beagle dog	Cynomolgus monkey	Rhesus monkey	Beagle dog
Ethoxyresorufin-O-deethylase[a, b]	1A2	10	1	6	11	14	2
Coumarin 7-hydroxylase[a, b]	2A6	5	1	0.2	2	1	0.2
Chlorzoxazone 6-hydroxylase[a]	2E1	1	0.5	0.5	NA	NA	NA
NDMA N-demethylase[b]	2E1	NA	NA	NA	1	1	1
Tolbutamide 4-hydroxylase[a, b]	2C9	0.5	0.4	0.0	0.6	0.5	0.0
Omeprazole 5-hydroxylase[a]	2C19	2	0.2	0.0	NA	NA	NA
S-mephenytoin 4'-hydroxylase[b]	2C19	NA	NA	NA	2	1	0.3
Dextromethorphan O-demethylase[a]	2D6	2	5	0.4	NA	NA	NA
Bufuralol 1'-hydroxylase[b]	2D6	NA	NA	NA	16	16	1
Midazolam 1'-hydroxylase[a]	3A4	1	1	1	4	3	3
Erythromycin N-demethylase[b]	3A4	NA	NA	NA	19	13	6
Omeprazole sulphoxidation[a]	3A4	1	0.2	0.1	NA	NA	NA

[a]Turpeinen et al. (2007); [b]Sharer et al. (1995).
CYP activity ratios (CYP_{animal}/CYP_{human}) with probe substrates. The colours - green, - yellow and - red indicate that there are minor (<5 and >0.2), medium (<10 and >5 or <0.2 and >0.1) or major differences (>10 or <0.1) in enzyme activity, respectively, in animals compared with humans. A fivefold or higher activity in the animal species compared with the activity in humans might result in an insufficient exposure of the drug candidate in the animal species. Also an activity which is only 0.2 (1/5) or less than that in humans could result in an insufficient exposure of metabolites in the animal species.

Clearance of compounds - species

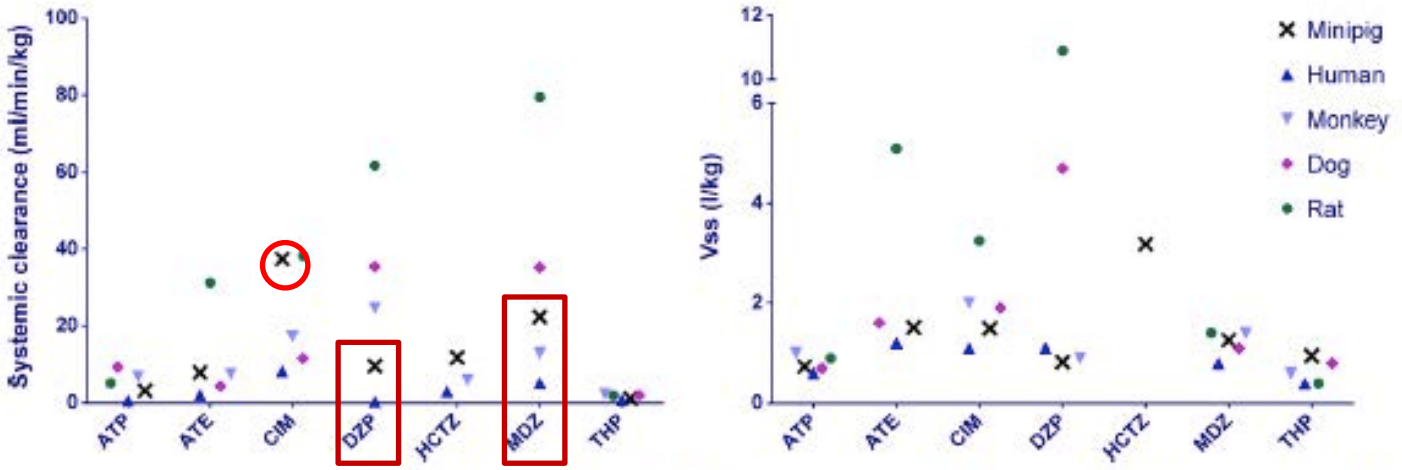
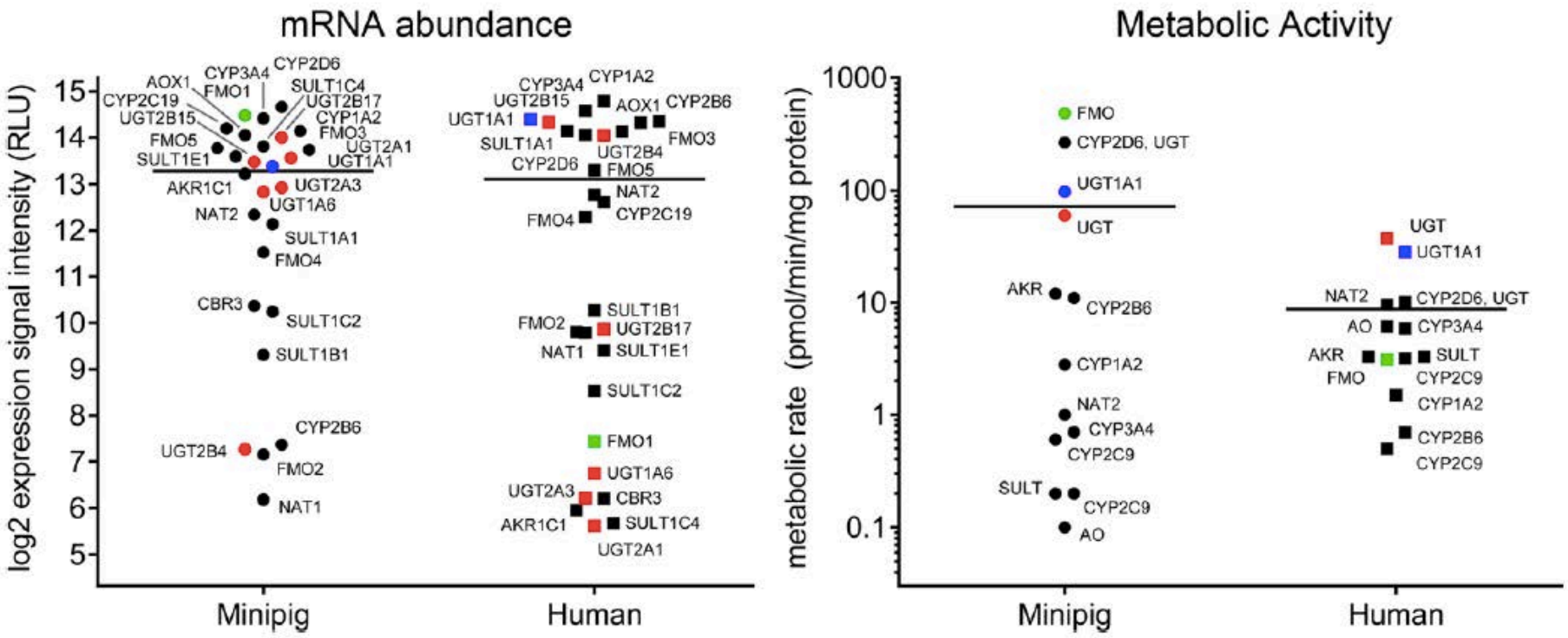


Fig. 3 Comparison of parameters values estimated by NCA analysis on the PK of antipyrine (ATP), atenolol (ATE), cimetidine (CIM), diazepam (DZP), hydrochlorothiazide (HCTZ), midazolam (MDZ) and theophylline (THP) in minipigs to values extracted from the literature for human, monkey, dog and rat. All data are available in Supplementary Material I.

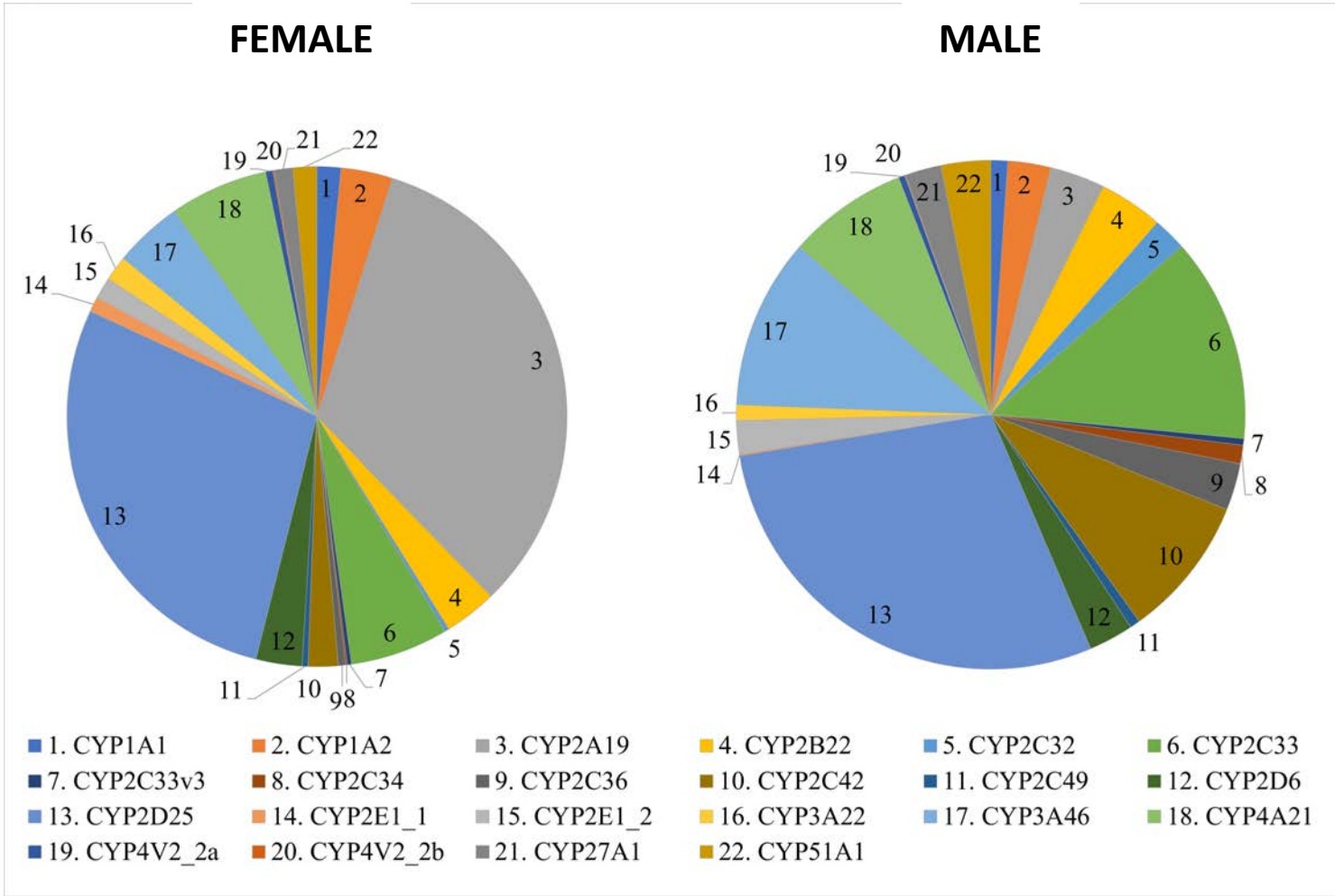
Lignet et al. Pharm Res. 2016, 33:2565-79.

mRNA abundance and activity data



Heckel et al. BMC Genomics. 2015, 16:932.

Protein abundance: gender differences



F > M : CYP1A1, CYP1A2, **CYP2A19**, CYP2E1_2, CYP3A22

Buyssens et al. under submission.

Göttingen Minipig: ideal animal model?

CYP	Rel. content in human liver (%)	Estim. fraction of drugs metabolized by indiv. CYP	Marker activity	Model system
1A2	12	4 %	caffeine	rat, rabbit, pig, minipig
2C9/10/19	20	11 %	diclofenac (2C9), (S)-mephenytoin (2C19)	monkey (*Maccacus mulatta*)
2D6	4	30 %	sparteine, debrisoquine, dextromethorphan	dog
2E1	6	2 %	chlorzoxazone	rat, rabbit, pig, minipig
3A4	30	52 %	nifedipine, erytromycin, alprazolam, dextrometorphan	pig, minipig

Zuber et al. J. Cell. Mol. Med. 2002, 6(2):189-198.

Further considerations

- Take into account pseudogenes. More prominent in dog than in Göttingen Minipig.
- Dogs no AOX, NAT1 ad NAT2 or CYP2C9-like enzymes => Göttingen Minipig better choice
- Pigs no PAPs
- Non-human primates not always a better reflection for man e.g. fosdevirine: cysteine conjugate metabolite linked to seizures
- Göttingen Minipig high glucuronidation and low sulphation compared to man

Species selection general tox studies

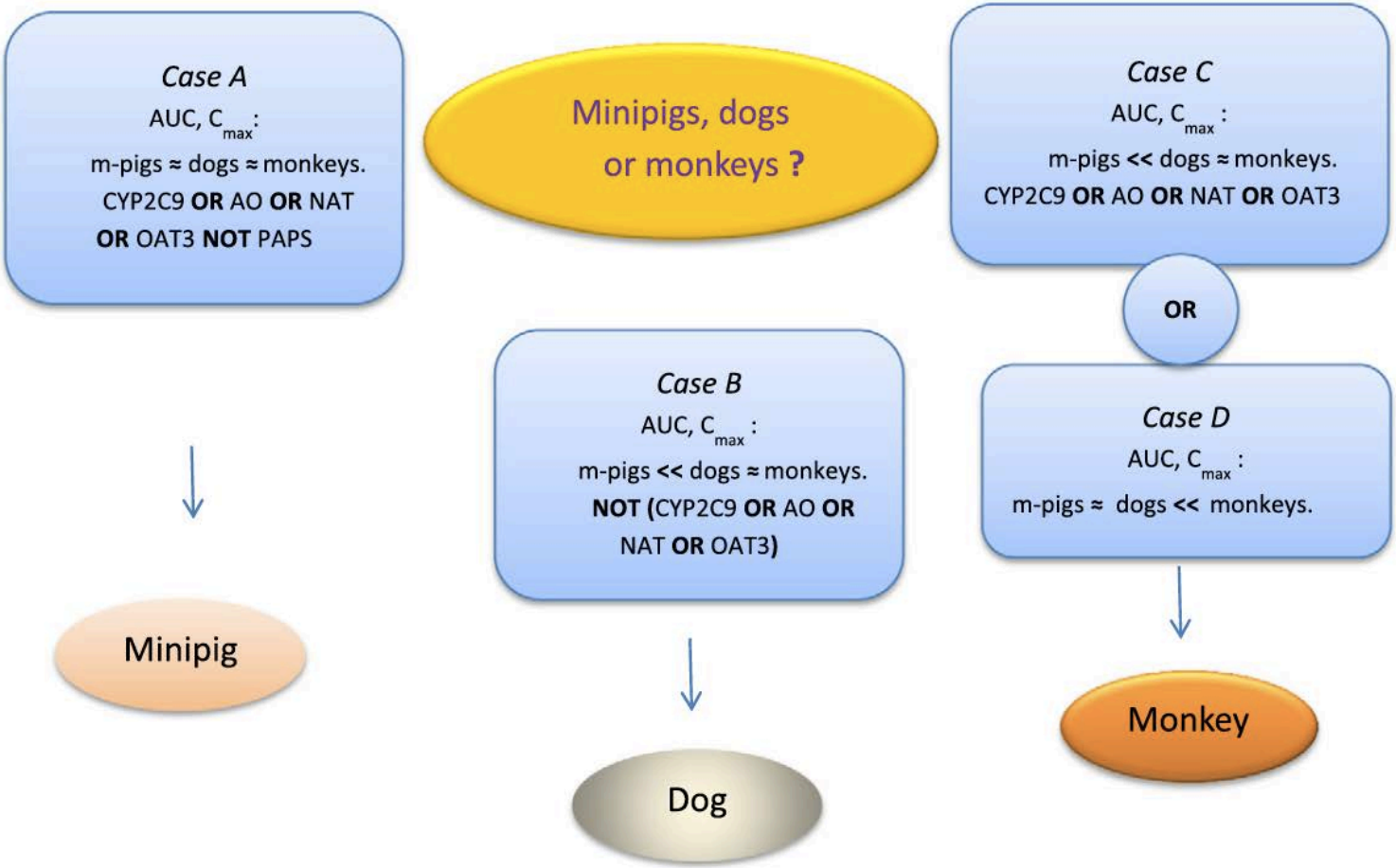


Fig. 2. Pharmacological relevant non-rodent species selection for toxicity studies.

Dalgaard et al. Journal of Pharmacological and Toxicological Methods. 2015, 74:80-92.

DMEs in paediatric/juvenile population: species comparison

Paediatric drug development

- 20% of European population is aged **less than 16** year
- Majority of medicines have **not** been tested in children
- **Differences** in drug safety profiles between mature and immature bodies
- January 2007: **Paediatric Regulation** No 1901/2006

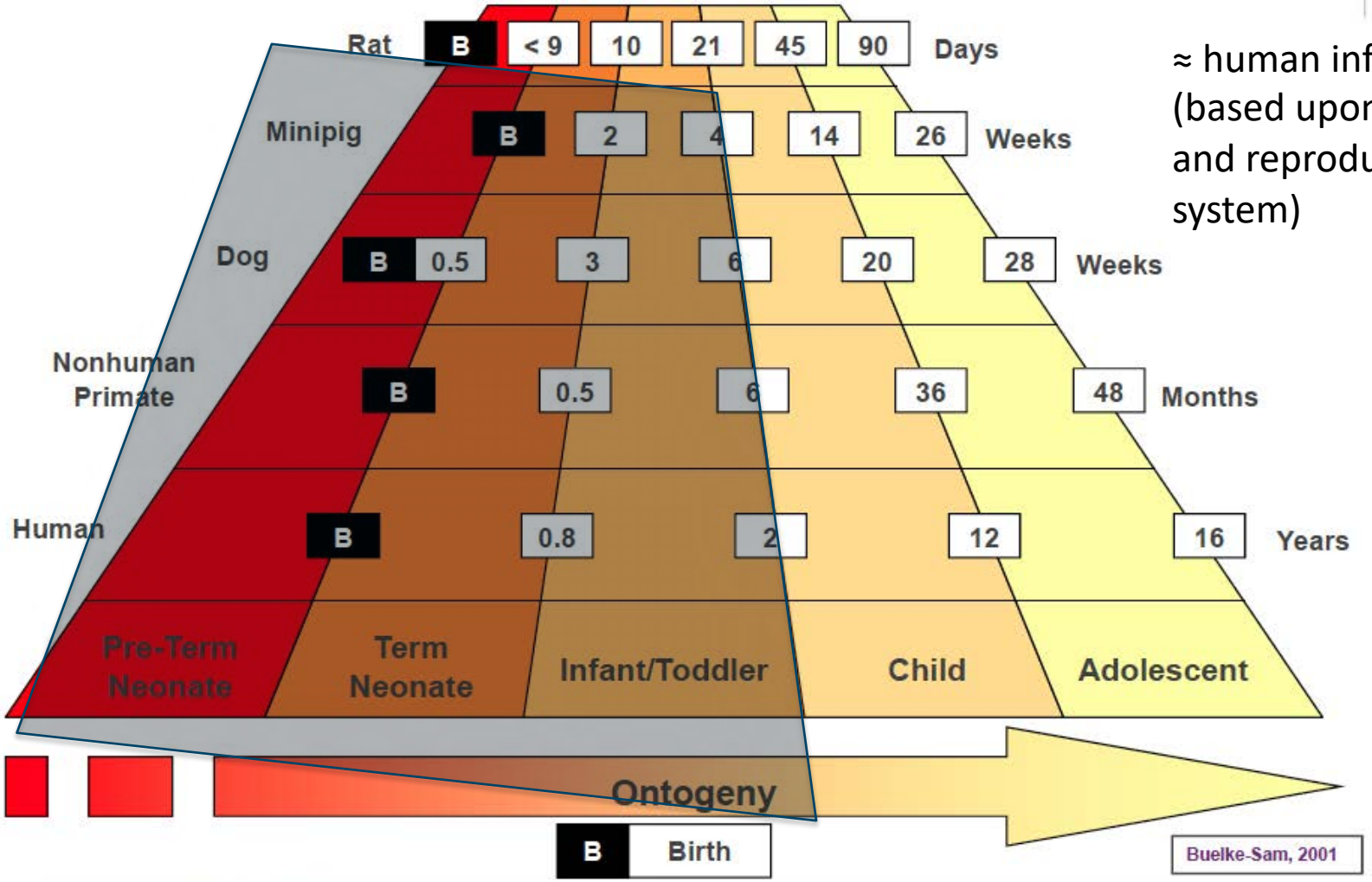
➔ safe and efficient drugs for children

Children ≠ adults
Neonate ≠ child

- Especially neonates and infants are of concern due to:
  - Prolonged gastric emptying time
  - Differences in gastric pH
  - High total water content
  - Less plasma protein binding
  - Decreased glomerular filtration rates
  - Immature drug metabolism and transport
  - …….

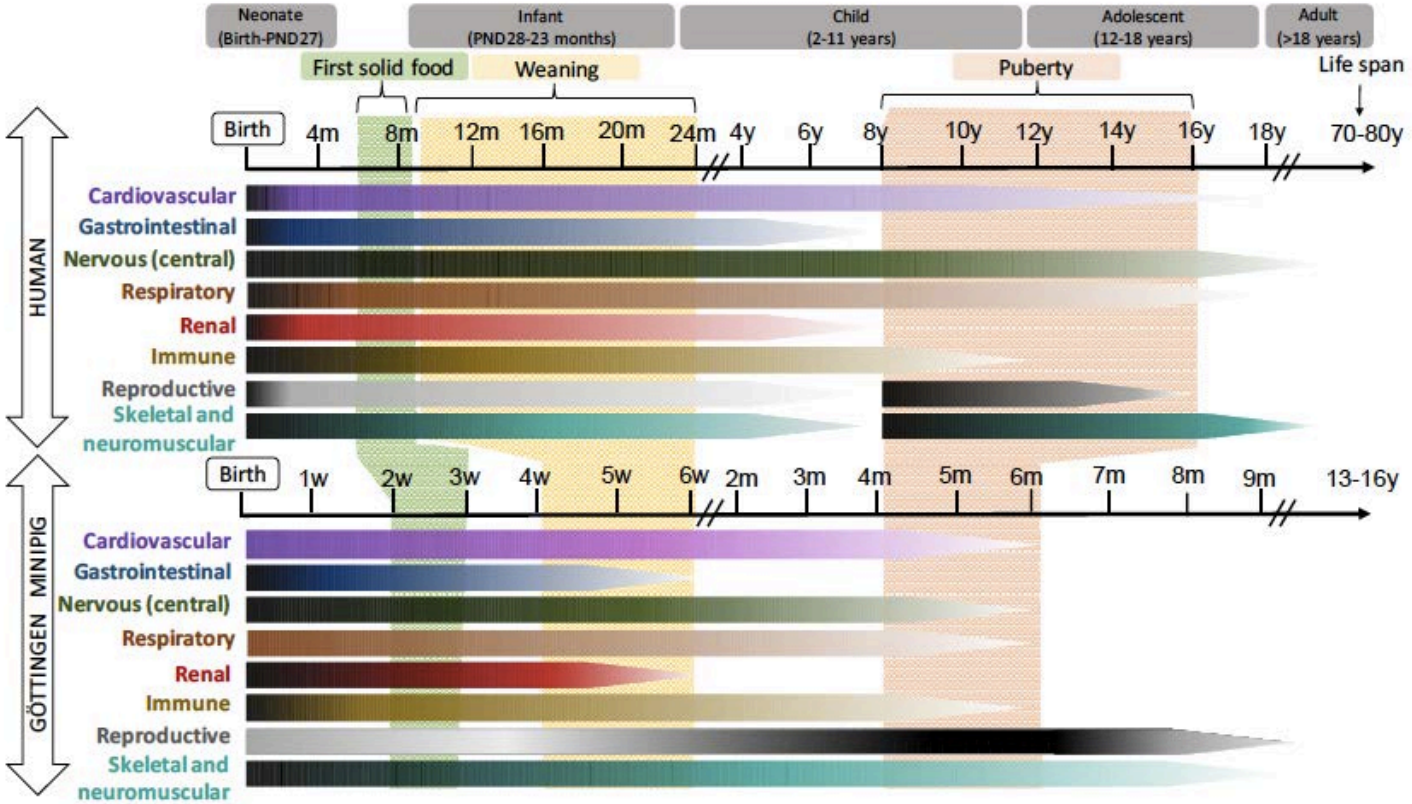
e.g. Gray baby syndrome

Corresponding age groups



≈ human infants (based upon CNS and reproductive system)

Corresponding age groups: organ systems



pharmaceutics

MDPI

Review

The Neonatal and Juvenile Pig in Pediatric Drug Discovery and Development

Miriam Ayuso [1,*], Laura Buyssens [1], Marina Stroe [1], Allan Valenzuela [1], Karel Allegaert [2,3,4], Anne Smits [3,5], Pieter Annaert [2], Antonius Mulder [6,7], Sebastien Carpentier [8], Chris Van Ginneken [1] and Steven Van Cruchten [1,*]

Corresponding age groups: organ systems

Species Comparison of Postnatal Bone Growth and Development

Tracey Zoetis,[1] Melissa S. Tassinari,[2] Cedo Bagi,[2] Karen Walthall,[1] and Mark E. Hurtt[2,*]
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Postnatal Anatomical and Functional Development of the Heart: A Species Comparison

Kok Wah Hew[1*] and Kit A. Keller[2]
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[2]Consultant, Washington DC

Landmarks in the Development of the Female Reproductive System

David A. Beckman[1*] and Maureen Feuston[2]
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[2]Sanofi-Synthelabo Research, Toxicology, Malvern, Pennsylvania

Development and Maturation of the Male Reproductive System

M. Sue Marty,[1*] Robert E. Chapin,[2] Louise G. Parks,[3] and Bjorn A. Thorsrud[4]
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[2]Pfizer Global Research & Development, Groton, Connecticut
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[4]Springborn Laboratories, Inc., Spencerville, Ohio

Species Comparison of Anatomical and Functional Renal Development

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Species Comparison of Anatomical and Functional Immune System Development

Michael P. Holsapple,[1*] Lori J. West,[2] and Kenneth S. Landreth[3]
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[2]The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada
[3]Department of Microbiology, Immunology and Cell Biology, West Virginia University, Morgantown, West Virginia

Species Comparison of Lung Development

Tracey Zoetis[1] and Mark E. Hurtt[2*]
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[2]Pfizer Global Research & Development, Groton, Connecticut

Species Comparison of Postnatal CNS Development: Functional Measures

Sandra L. Wood,[1*] Bruce K. Beyer,[2] and Gregg D. Cappon[3]
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[2]Sanofi-Synthelabo Research, Malvern, Pennsylvania
[3]Pfizer Global Research and Development, Groton, Connecticut

Postnatal Growth and Morphological Development of the Brain: A Species Comparison

Rebecca E. Watson,[1] John M. DeSesso,[1] Mark E. Hurtt,[2] and Gregg D. Cappon[2*]
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[2]Pfizer Global Research and Development, Groton, Connecticut

Postnatal Development of the Gastrointestinal System: A Species Comparison

Karen Walthall,[1] Gregg D. Cappon,[2] Mark E. Hurtt[2*] and Tracey Zoetis[3]
[1]Aclairo Pharmaceutical Development Group, Inc., Sterling, Virginia
[2]Pfizer Global Research and Development, Groton, Connecticut
[3]SciLucent, LLC, Herndon, Virginia

Corresponding age groups: organ systems

Consideration of the Development of the Gastrointestinal Tract in the Choice of Species for Regulatory Juvenile Studies

Noel John Downes

Species Differences in Renal Development and Associated Developmental Nephrotoxicity

Kendall S. Frazier

Species Comparison of Postnatal Development of the Female Reproductive System

Susan B. Laffan*[1], Lorraine M. Posobiec[1], Jenny E. Uhl[1], and Justin D. Vidal[2]

Pre- and Postnatal Lung Development: An Updated Species Comparison

Geertje Lewin*[1] and Mark E. Hurtt[2]

Comparative Aspects of Pre- and Postnatal Development of the Male Reproductive System

Catherine A. Picut*[1], Mary K. Ziejewski[2], and D. Stanislaus[2]

Pre- and Postnatal Development of the Eye: A Species Comparison

Steven Van Cruchten*[1], Vanessa Vrolyk[2], Marie-France Perron Lepage[3], Marie Baudon[3], Hélène Voute[3], Sabine Schoofs[4], Julius Haruna[5], Marie-Odile Benoit-Biancamano[2], Benoît Ruot[3], and Karel Allegaert[6,7]

Prenatal and postnatal development of the mammalian ear

Nicola Powles-Glover[1] | Mark Maconochie[2]

Ontogeny of DMEs and DTS

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ASSOCIATE EDITOR: HYUNYOUNG JEONG

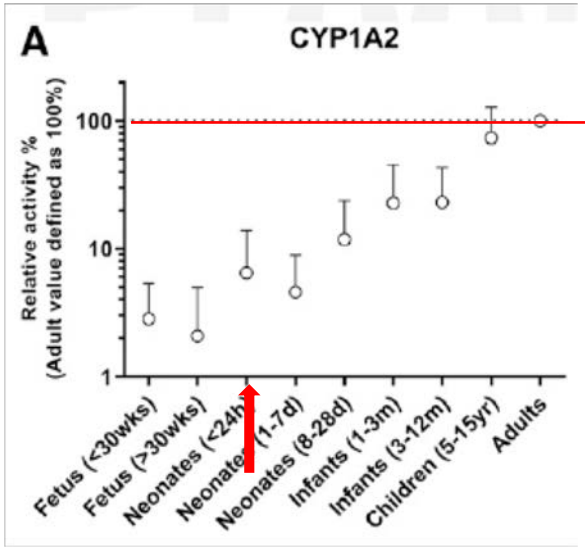
Ontogeny of Hepatic Transporters and Drug-Metabolizing Enzymes in Humans and in Nonclinical Species[S]

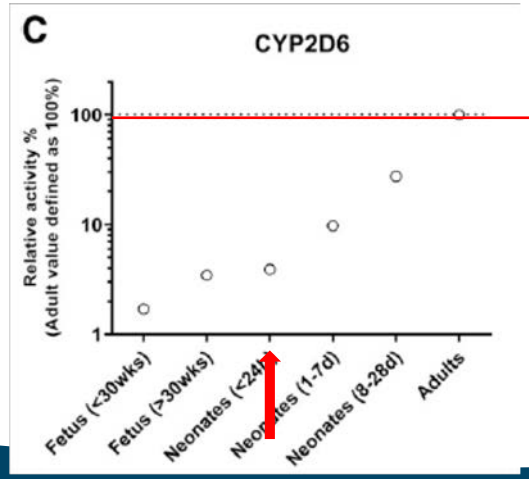
B. D. van Groen, J. Nicolaï, A. C. Kuik, S. Van Cruchten, E. van Peer, A. Smits, S. Schmidt, S. N. de Wildt, K. Allegaert, L. De Schaepdrijver, P. Annaert,[1] and J. Badée[1]

Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands (B.D.v.G., K.A.); Development Science, UCB BioPharma SRL, Braine-l'Alleud, Belgium (J.N.); Leiden Academic Center for Drug Research, Leiden University, Leiden, The Netherlands (A.C.K.); Department of Veterinary Sciences, Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, Wilrijk, Belgium (S.V.C.); Fendigo sa/nvbv, An Alivira Group Company, Brussels, Belgium (E.v.P.); Department of Development and Regeneration KU Leuven, Leuven, Belgium (A.S.); Neonatal intensive care unit, University Hospitals Leuven, Leuven, Belgium (A.S.); Department of Pharmaceutics, Center for Pharmacometrics and Systems Pharmacology, College of Pharmacy, University of Florida, Orlando, Florida (S.S.); Department of Pharmacology and Toxicology, Radboud Institute of Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands (S.N.d.W.); Departments of Development and Regeneration and of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium (K.A.); Department of Hospital Pharmacy, Erasmus MC, University Medical Center, Rotterdam, The Netherlands (K.A.); Nonclinical Safety, Janssen R&D, Beerse, Belgium (L.D.S.); Drug Delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium (P.A.); and Department of PK Sciences, Novartis Institutes for BioMedical Research, Basel, Switzerland (J.B.)

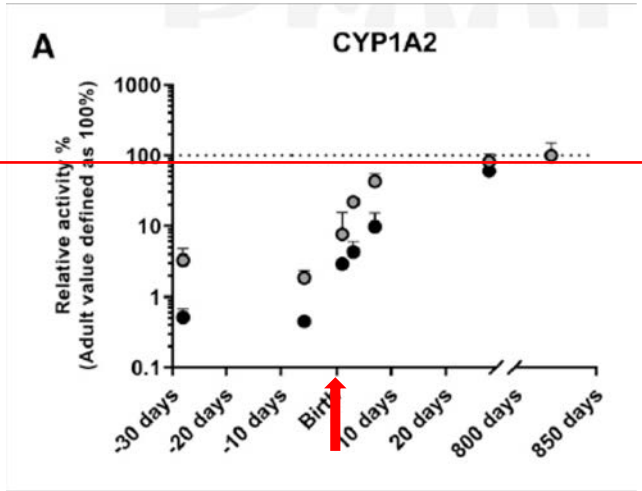
Ontogeny profiles of CYP450 activity

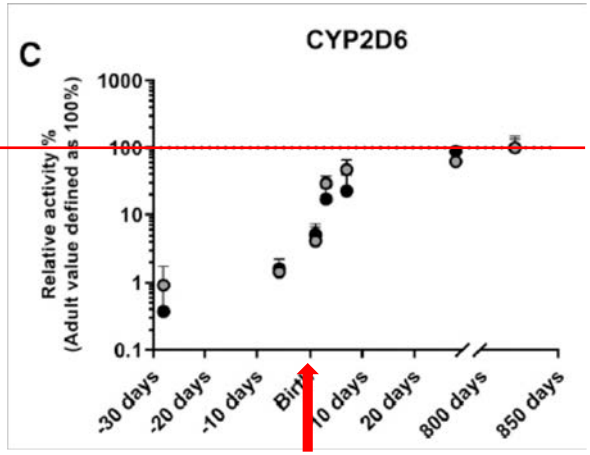
HUMAN



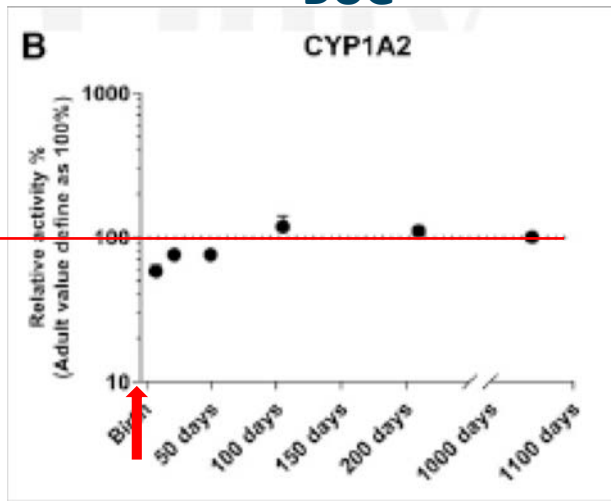


GÖTTINGEN MINIPIG





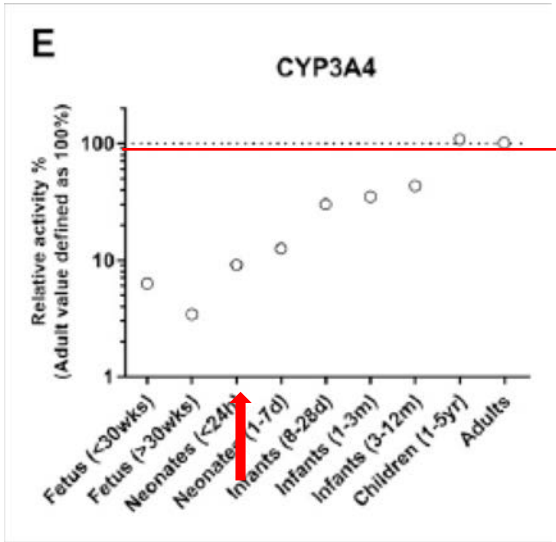
DOG



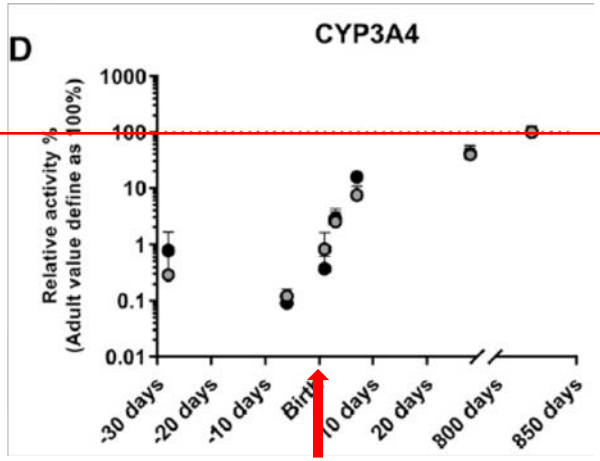
CYNO?

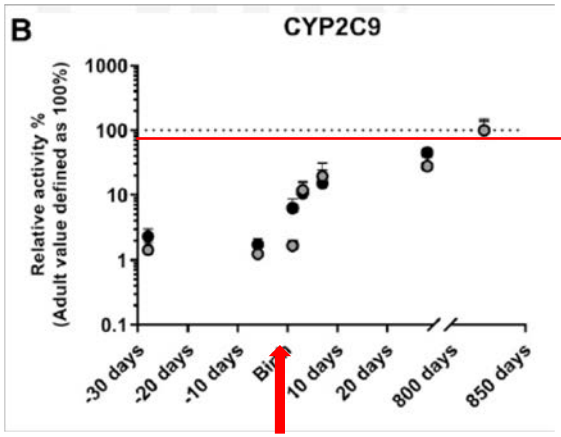
Ontogeny profiles of CYP450 activity

HUMAN



GÖTTINGEN MINIPIG





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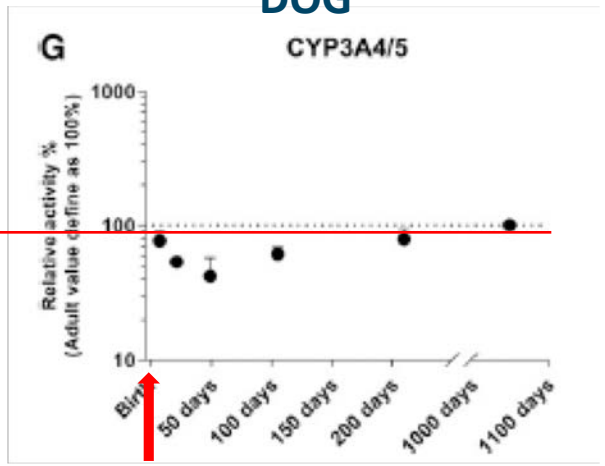
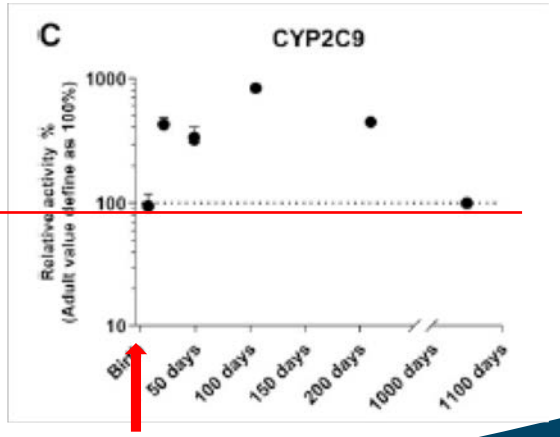
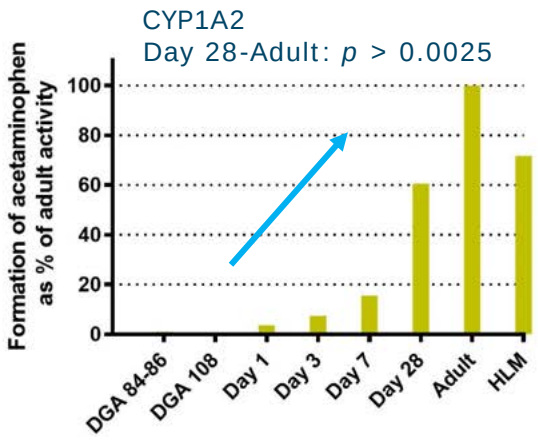


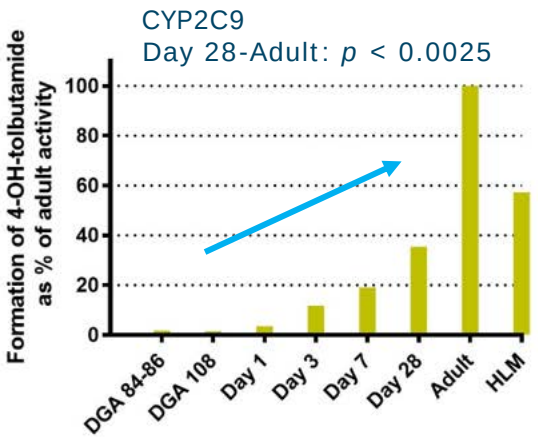


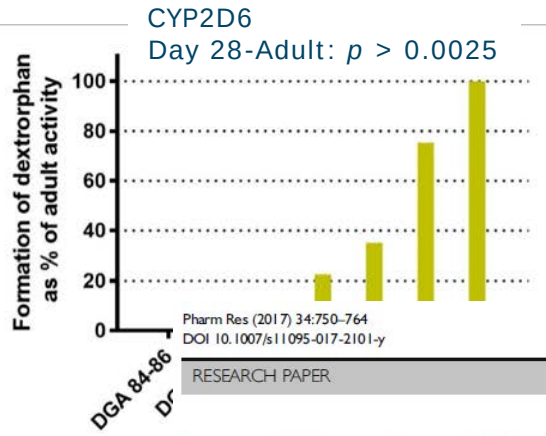
Onset of CYP activity in Göttingen Minipig

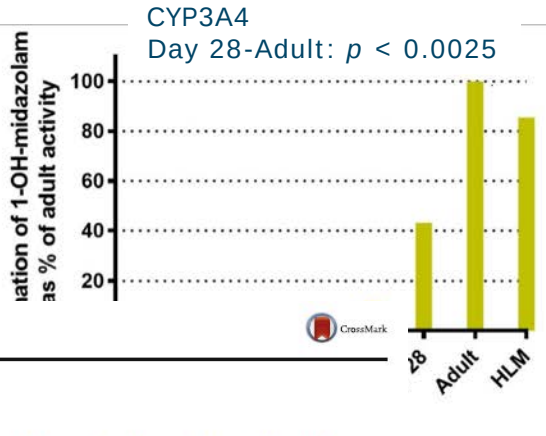
FAST: CYP1A2 and CYP2D6

SLOW: CYP2C9 and CYP3A4









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

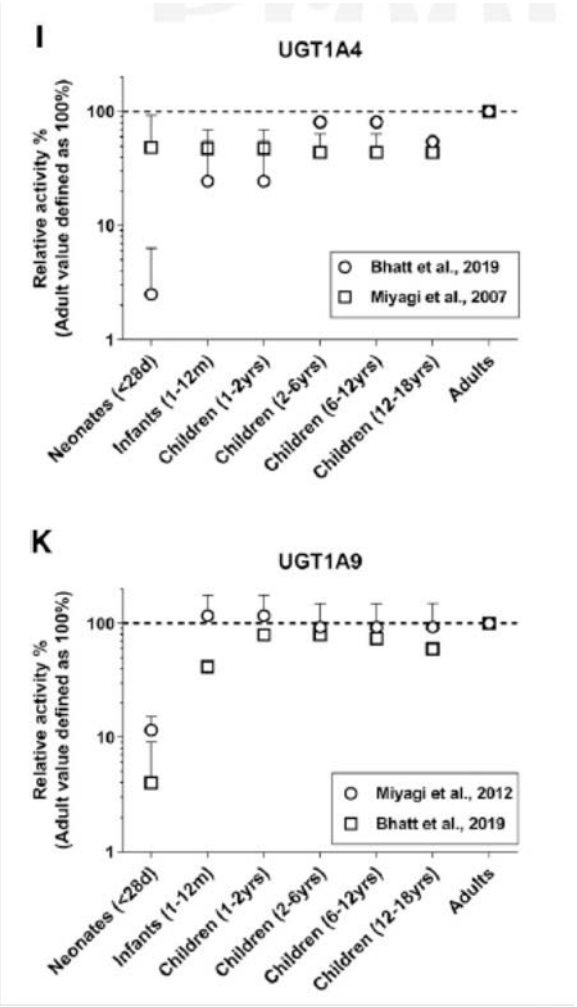
RESEARCH PAPER

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

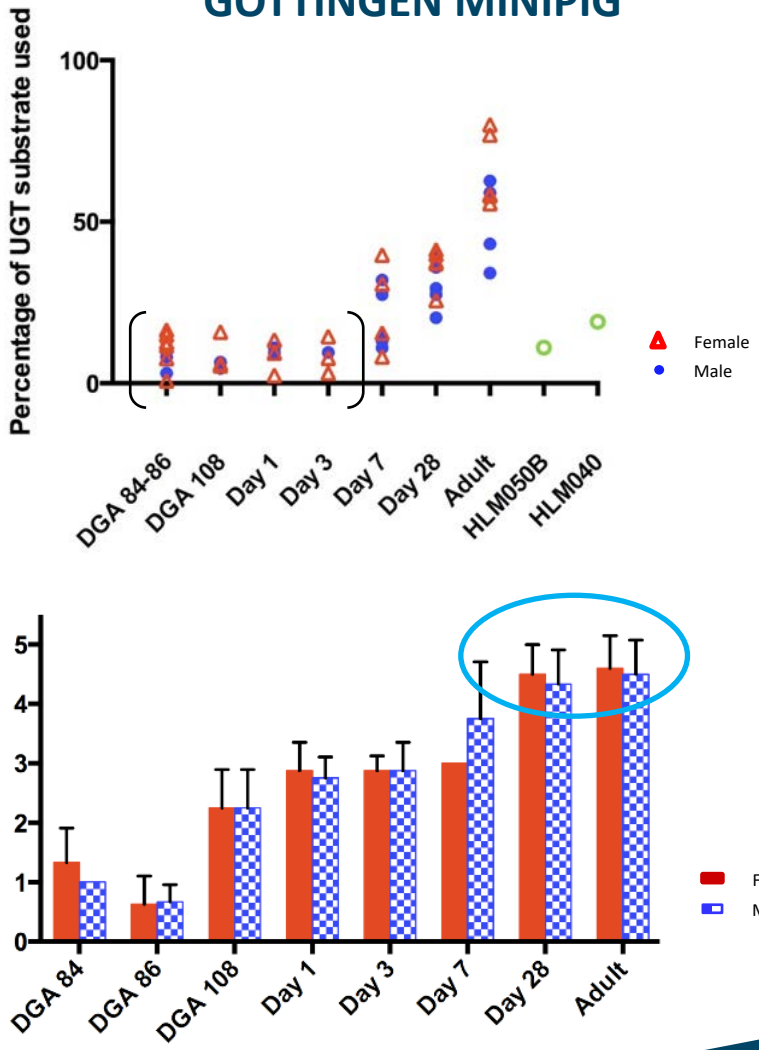
Els Van Peer[1] • Frank Jacobs[2] • Jan Snoeys[2] • Jos Van Houdt[2] • Ils Pijpers[2] • Christophe Casteleyn[1] • Chris Van Ginneken[1] • Steven Van Cruchten[1]

Ontogeny profiles of UGT activity

HUMAN



GÖTTINGEN MINIPIG



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

ORIGINAL PAPER

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

Els Van Peer[1] · Noel Downes[2] · Christophe Casteleyn[1] · Chris Van Ginneken[1] · Arie Weeren[3] · Steven Van Cruchten[1]

Journal of Pharmacological and Toxicological Methods 62 (2010) 196–220

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

ELSEVIER

Original article

The utility of the minipig as an animal model in regulatory toxicology☆

Gerd Bode[a,*], Peter Clausing[b], Frederic Gervais[c], Jeanet Loegsted[d], Jörg Luft[e], Vicente Nogues[f], Jennifer Sims[g] and under the auspices of the Steering Group of the RETHINK Project

BCPT Basic & Clinical Pharmacology & Toxicology, 2014, 114, 387–394

Doi: 10.1111/bcpt.12173

Ontogeny of CYP3A and P-Glycoprotein in the Liver and the Small Intestine of the Göttingen Minipig: An Immunohistochemical Evaluation

Els Van Peer, Evy Verbucken, Moayad Saad, Christophe Casteleyn, Chris Van Ginneken and Steven Van Cruchten

Applied Veterinary Morphology, Department of Veterinary Sciences, University of Antwerp, Wilrijk, Belgium

(Received 12 September 2013; Accepted 29 October 2013)

BCPT Basic & Clinical Pharmacology & Toxicology, 2015, 117, 350–357

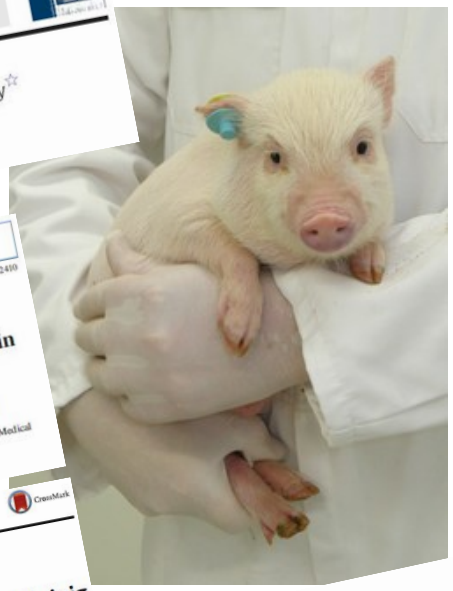
Doi: 10.1111/bcpt.12410

Age-related Differences in CYP3A Abundance and Activity in the Liver of the Göttingen Minipig

Els Van Peer[1], Lies De Bock[2], Koen Bousery[2], Jan Van Bocxlaer[2], Christophe Casteleyn[1], Chris Van Ginneken[1] and Steven Van Cruchten[1]

[1]Applied Veterinary Morphology, Department of Veterinary Sciences, University of Antwerp, Wilrijk, Belgium and [2]Laboratory of Medical Biochemistry and Clinical Analysis, Department of Bioanalysis, Ghent University, Ghent, Belgium

(Received 11 February 2015; Accepted 12 April 2015)



Pharm Res (2016) 33:2565–2579
DOI 10.1007/s11095-016-1982-5

RESEARCH PAPER

Characterization of Pharmacokinetics in the Göttingen Minipig with Reference Human Drugs: An *In Vitro* and *In Vivo* Approach

Floriane Lignet[1] · Eva Sherbetjian[1] · Nicole Kratochwil[1] · Russell Jone · Michael B. Otteneder[1] · Thomas Singer[1] · Neil Parrott[1]

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

Els Van Peer[1] · Frank Jacobs[2] · Jan Snoeys[2] · Jos Van Houdt[2] · Ils Pijpers[2] · Christophe Casteleyn[1] · Chris Van Ginneken[1] · Steven Van Cruchten[1]

Received: 5 August 2016 / Accepted: 6 January 2017 / Published online: 17 January 2017

Science+Business Media New York 2017

Conclusions SMEs

- Gene expression levels of major hepatic DMEs similar in Göttingen Minipig and man, but isoform-specific differences occur (e.g. UGT1A6, UGT2A1, UGT2A3, UGT2B17, FMO1, AKR1C1, CBR3, SULT1C4 and SULT1E1 higher mRNA expression in Göttingen Minipig)

- Ontogeny of CYPs and UGTs similar pattern in juvenile Göttingen Minipigs compared to the paediatric populations

PK of SMEs in paediatric disease models

frontiers in Pharmacology

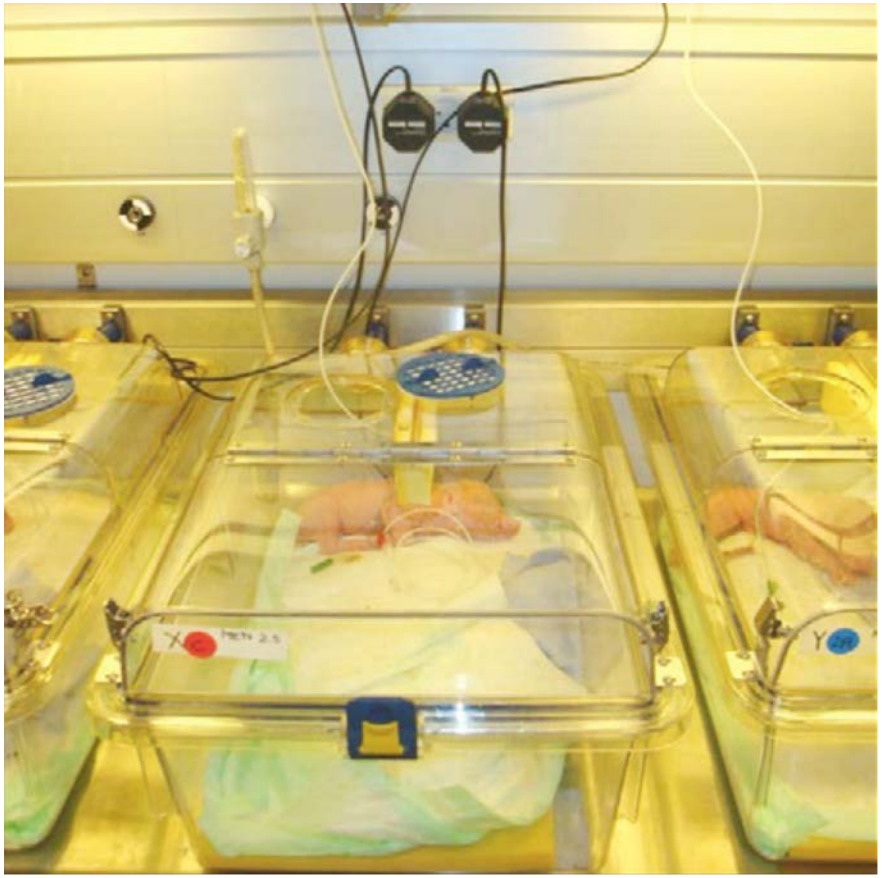
REVIEW
published: 13 May 2020
doi: 10.3389/fphar.2020.00587

A Physiology-Based Pharmacokinetic Framework to Support Drug Development and Dose Precision During Therapeutic Hypothermia in Neonates

Anne Smits[1,2*], Pieter Annaert[3], Steven Van Cruchten[4] and Karel Allegaert[2,5,6]

[1] Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium, [2] Department of Development and Regeneration, KU Leuven, Leuven, Belgium, [3] Drug Delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [4] Applied Veterinary Morphology, Department of Veterinary Sciences, University of Antwerp, Wilrijk, Belgium, [5] Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [6] Department of Clinical Pharmacy, Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands

OPEN ACCESS



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

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

↓

PBPK model

PK of ASOs in juvenile Göttingen Minipigs

OXFORD SOT Society of Toxicology
www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 157(1), 2017, 112–128
doi: 10.1093/toxsci/kfx025
Advance Access Publication Date: January 25, 2017
Research article

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†

Gene expression profiling of key nucleases in the juvenile Göttingen minipig

Allan Paulo Valenzuela[1,*], Laura Buyssens[1], Chloé Bars[1], Miriam Ayuso[1], Chris Van Ginneken[1], Neil Parrott[2], Yann Tessier[2], Georg Schmitt[2], Paul Barrow[2], Steven Van Cruchten[1]

[1] *Applied Veterinary Morphology, Department of Veterinary Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Antwerp, Belgium*
[2] *Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124 CH-4070 Basel, Switzerland*

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

No overt toxicity

GENERAL CONCLUSIONS

- Drug metabolism of small molecule drugs in neonatal and juvenile Göttingen Minipigs ≈ paediatric population
- Also a valuable model for new modalities such as ASOs
- Opportunities for assessment of covariates in juvenile Göttingen Minipig disease models that cannot be addressed in a clinical setting

ACKNOWLEDGEMENTS

ELLEGAARD GÖTTINGEN MINIPIGS

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

GHENT UNIVERSITY

Roche

sequani NON CLINICAL great people, great work, real results

KU LEUVEN

ePTRI EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE

fwo Research Foundation Flanders Opening new horizons

QUESTIONS?

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