

Pigs in research

What about the piglet



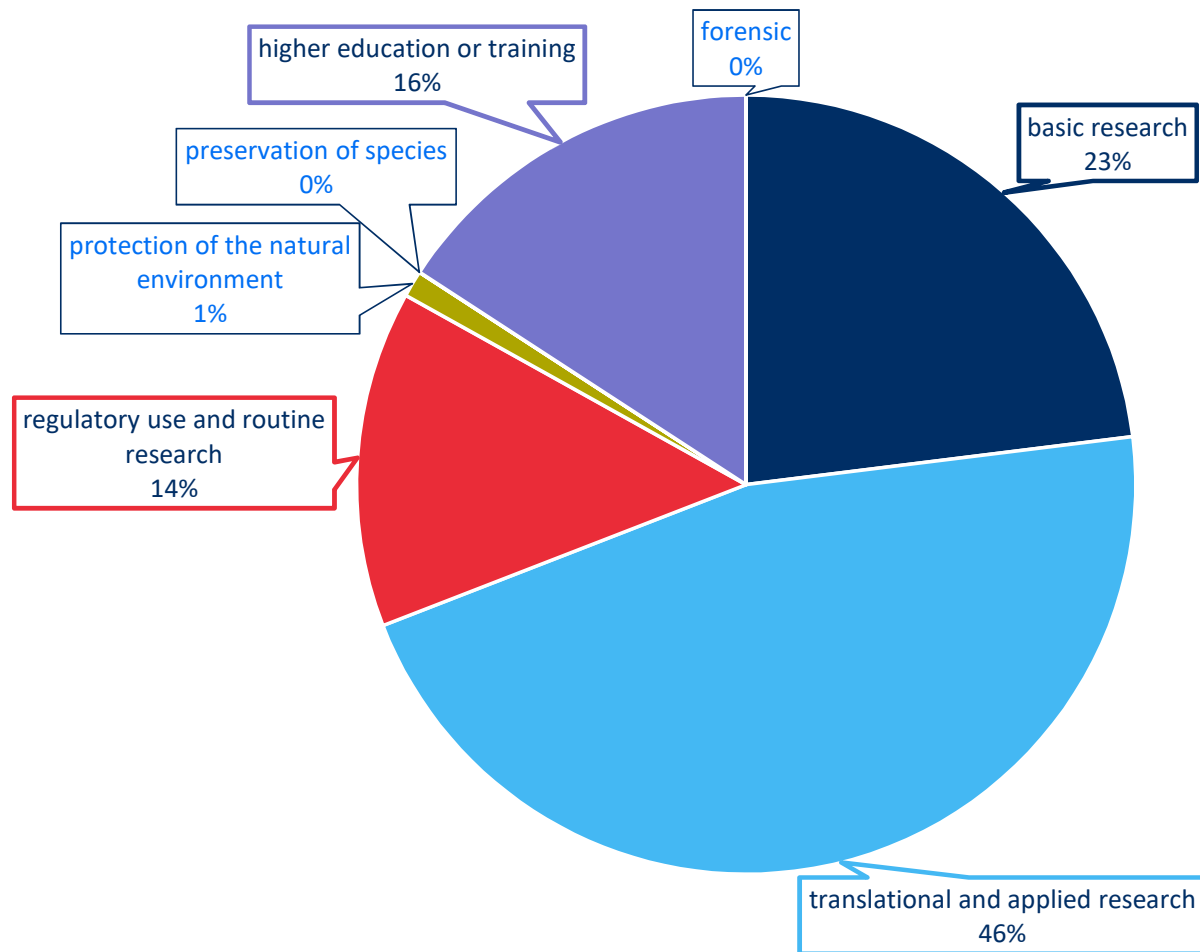
Content

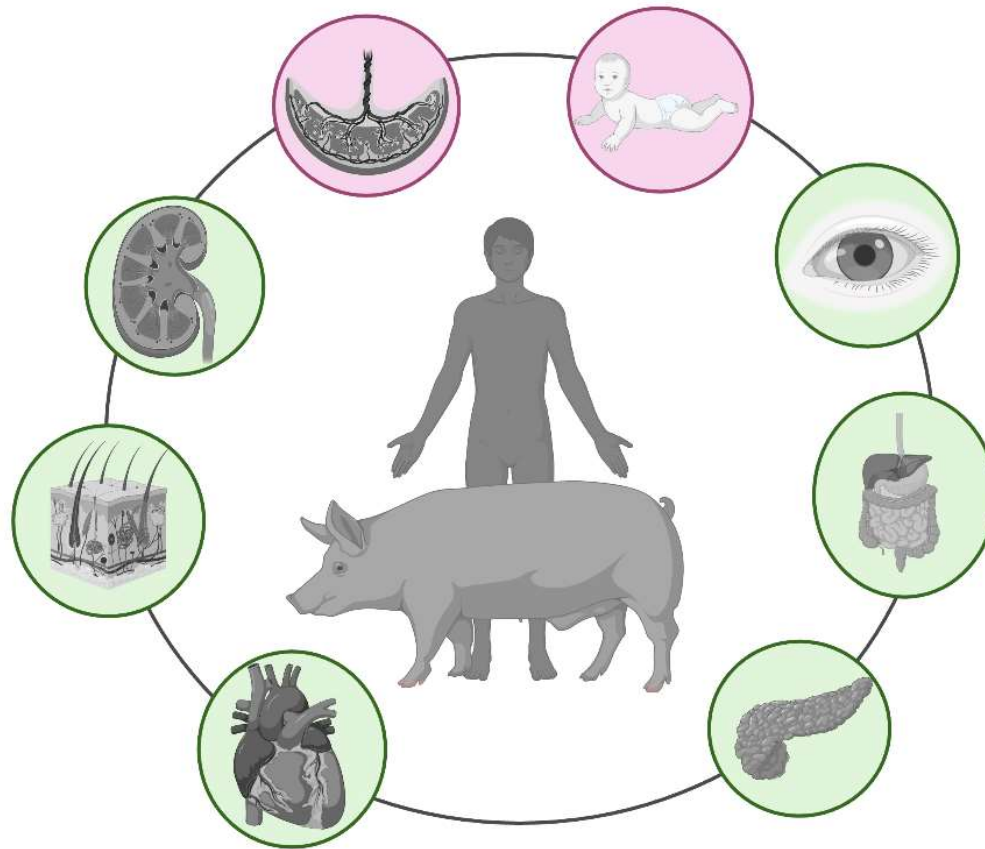
0. Introduction

I. Preterm piglet

II. Low birth weight piglet – IUGR

III. Neonatal – juvenile piglet





Smith & Swindle, ILAR, 2006
Zettler et al. 2020 Animal Reproduction

The laboratory swine

- **Social animals**

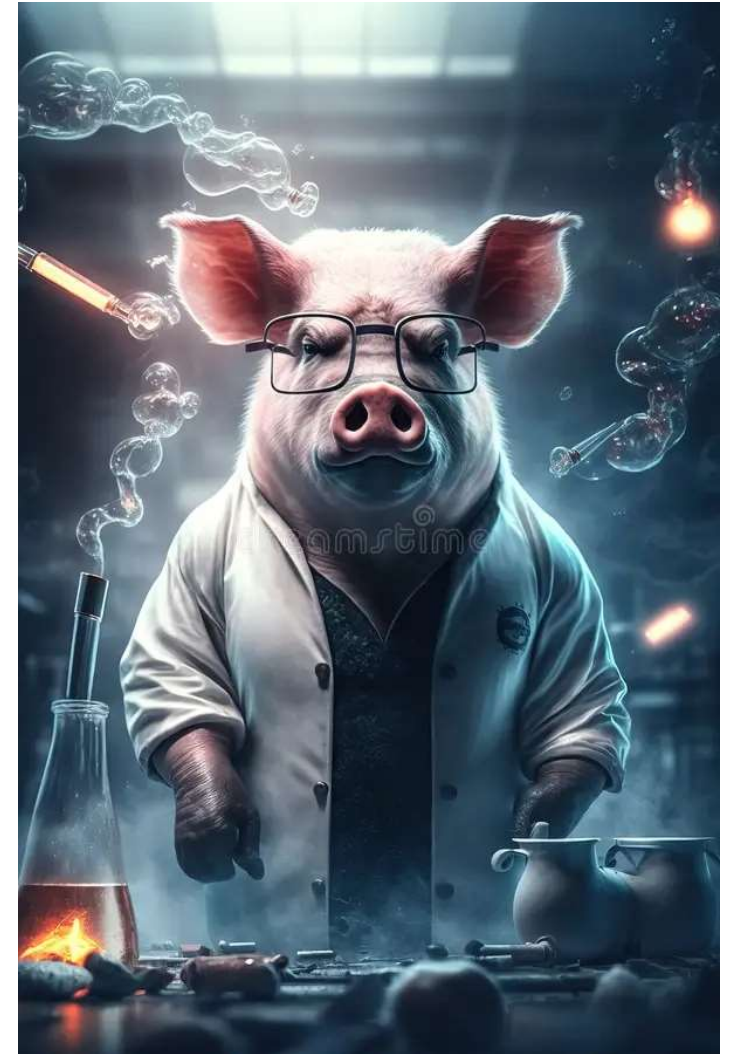
- Groups of females with young – dominance
- Adult boars – solitary
- Group max 10-15 animals
 - Minimize re-grouping

- **Intelligent**

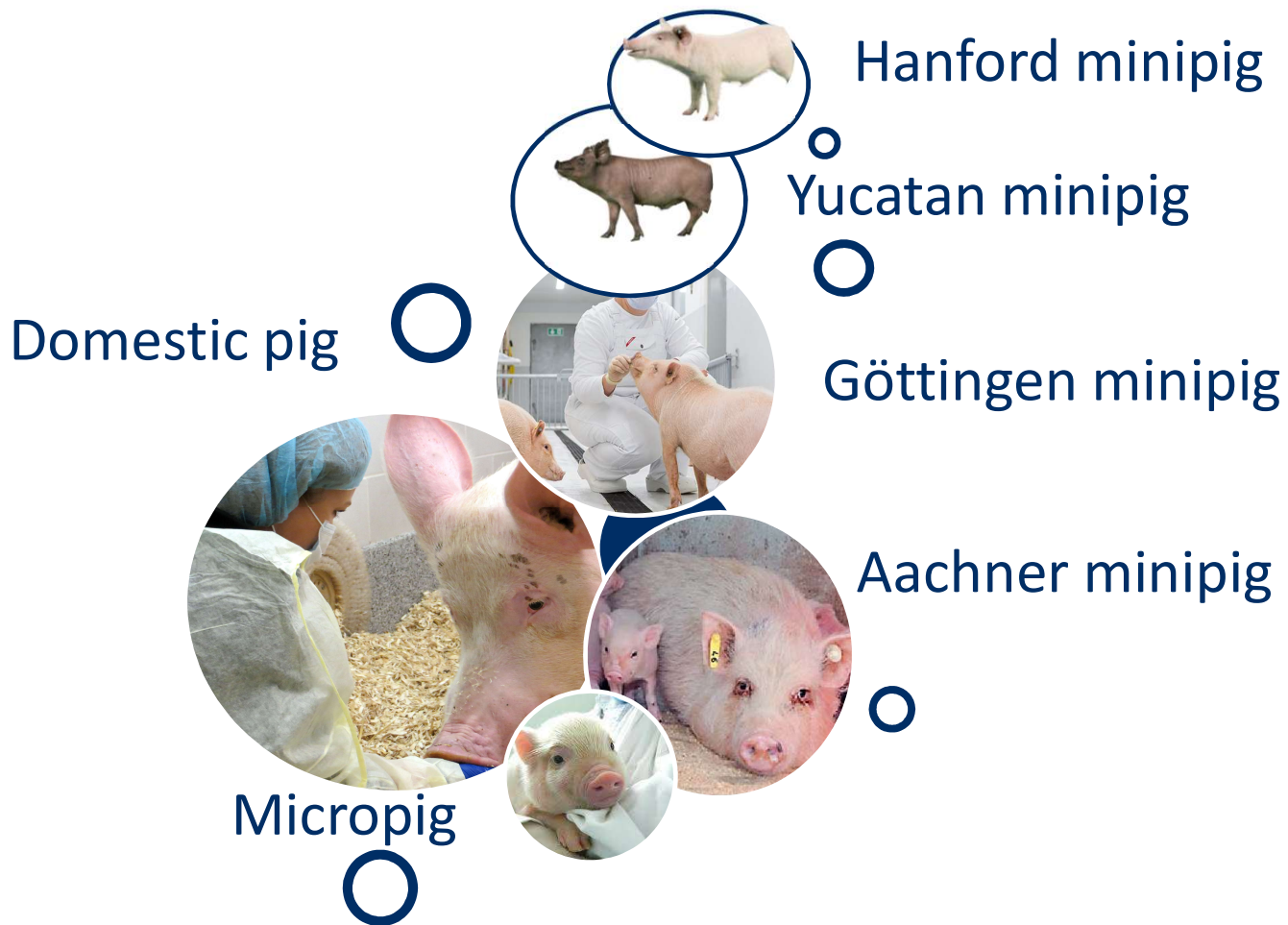
- Training – positive reinforcement, gentle handling
- Animal-centered research

- **Husbandry – transportation**

- Acclimatization after transport 1 wk
- Rooting (floor !), chewing, and rubbing



Bollen et al. The laboratory Swine 2010
Smith & Swindle, ILAR, 2006



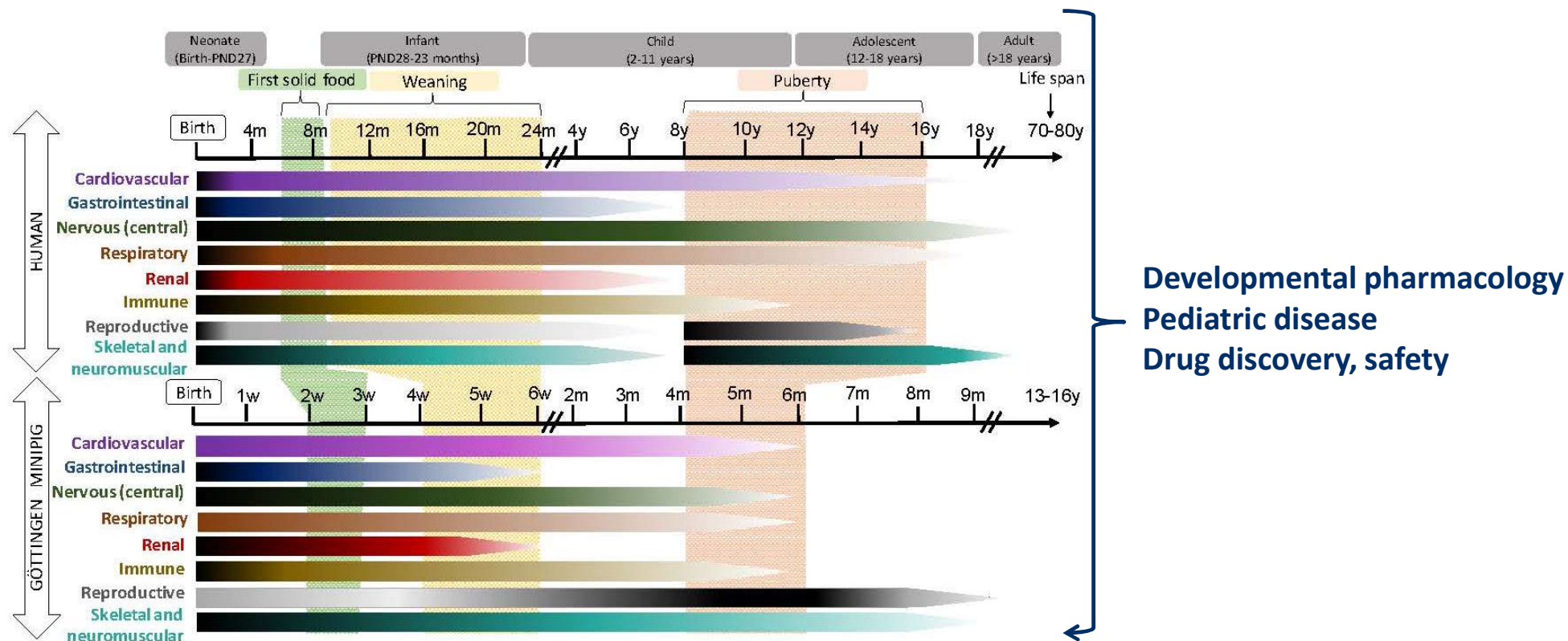


Figure 1. Schematic representation of the postnatal development of different organ systems in human (top) and Götting Minipig. In the horizontal bars, the intensity of the maturation process is represented by dark (more intense) and light (less intense) tones. The time bar represents weeks (w), months (m) or year (y) of life.

Content

0. Introduction

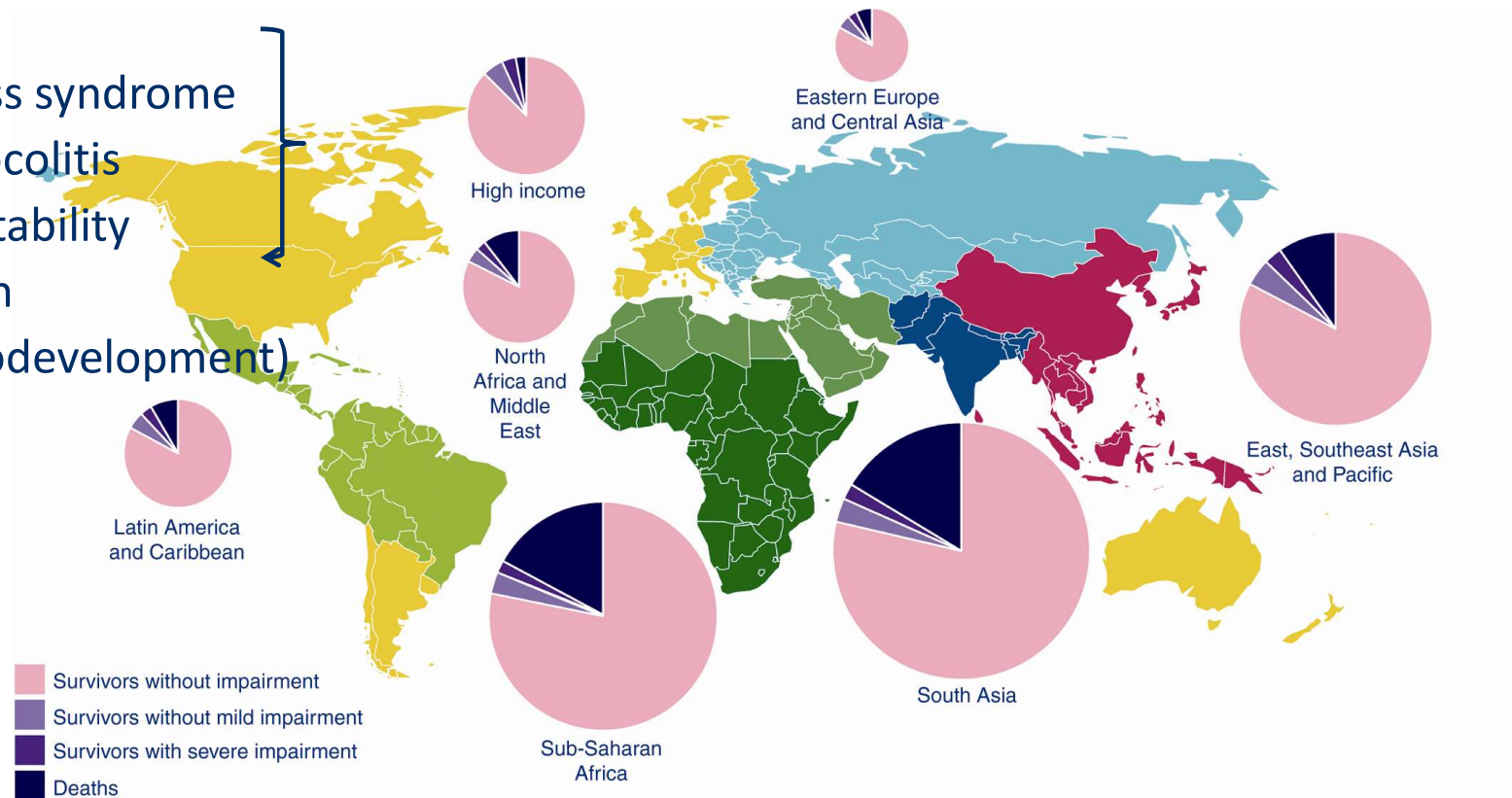
I. Preterm piglet

II. Low birth weight piglet – IUGR

III. Neonatal – juvenile piglet

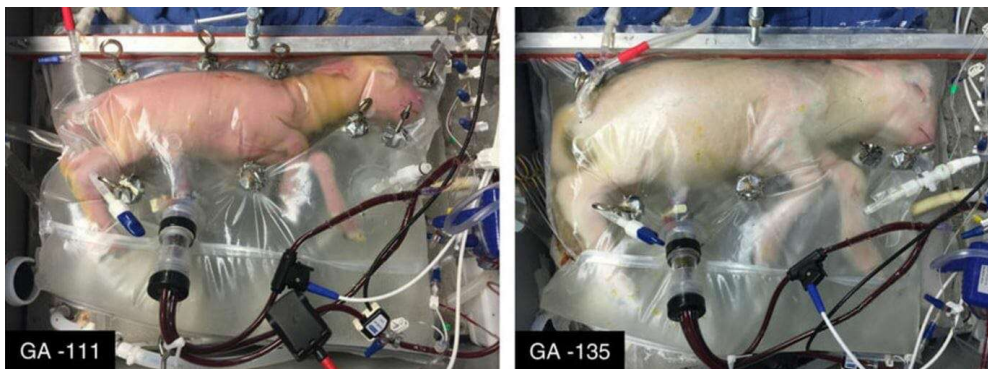
Preterm

- Respiratory distress syndrome
- Necrotizing enterocolitis
- Cardiovascular instability
- Suboptimal growth
- Brain injury (neurodevelopment)



Preterm

- “Model for human preterm physiology should produce viable neonates with maturation characteristics similar to the very preterm infant and have a body size that allows comparative monitoring, sampling and clinical interventions.” Eiby et al. 2013 PLoSOne, e68763



Partridge et al. 2017, Nature Communications







	Viable preterm newborns ↓↓↓	Term birth ↓	Weaning transition ↓↓↓	Life span ↓
Rat pup	 94-97% gestation	22 d gestation	 170-190% gestation	2-3 years
Piglet	 90-95% gestation	116 d gestation	 120-140% gestation	13-16 years
Infant	 70-90% gestation	280 d gestation	 110-140% gestation	70-80 years

Figure 1. Maturation (as percentage of gestation) of lungs, gut, and brain relative to term birth, weaning, and total life span for rats, pigs, and humans. Symbols for lungs, gut, and brain indicate the time period when ontogenetic maturation is sufficient to secure general viability of preterm newborns (dark grey boxes), that is, independent breathing (determined by lung alveolar respiration), digestion of nonmilk food (determined by gut functions), and locomotion (in part determined by brain motoric control). See online version for figure in color.

Sangild et al. 2013 J Animal Sci

Preterm piglet

- **90% of gestation – domestic sow**
 - 101-104 d ~ preterm infant > 32 wks
 - 97 d ~ preterm infant 28-30 wks
 - 91-94 d ~ preterm infant 23-25 wks
- **Caeserean section (vaginal delivery – farrowing induction)**
- **! Need for colostrum – maternal plasma**
- **Neonatal intensive care needed**
 - Oxygen and heat
 - Minimal enteral feeding (NEC)
 - Parenteral feeding
 - Similar 'body dimensions' (400-500 gr)
- **Rapid development**
- **Humane endpoints**



Similar perinatal brain growth spurt, similar patterns of cellular development and myelination, presence of gyri and sulci, impaired neurodevelopment (delayed coordination, learning)

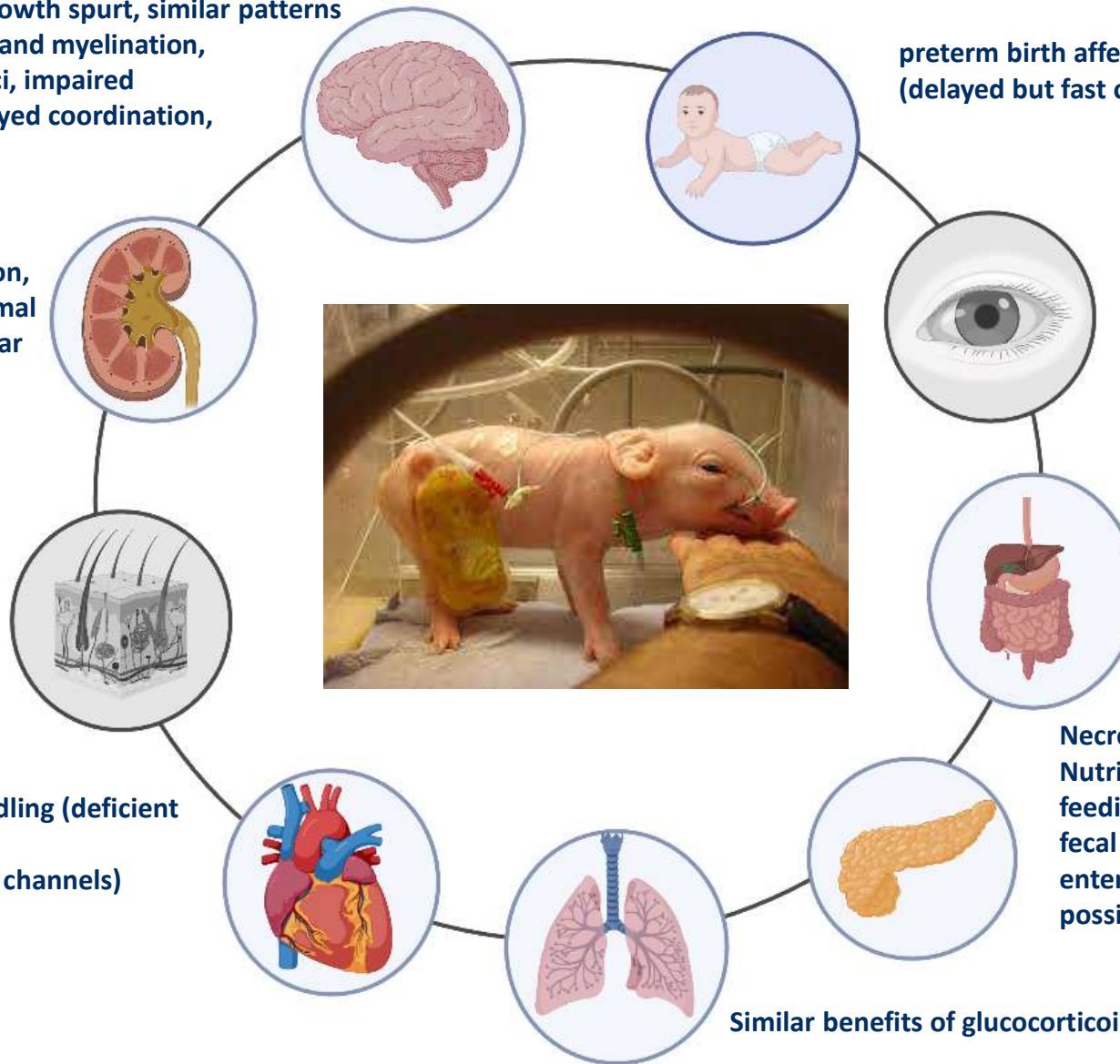
preterm birth affects early motor development (delayed but fast catch-up)

Renal injury and inflammation, increased percentage abnormal glomeruli, reduced glomerular area

Immature calcium handling (deficient developmental pattern of expression of cation channels)

Necrotizing enterocolitis model – SBS model
Nutritional interventions (incl parenteral feeding, fecal transplants, pro- and prebiotics, minimal enteral feeding, growth factors (eg GLP-2)) possible

Similar benefits of glucocorticoid exposure



Content

0. Introduction

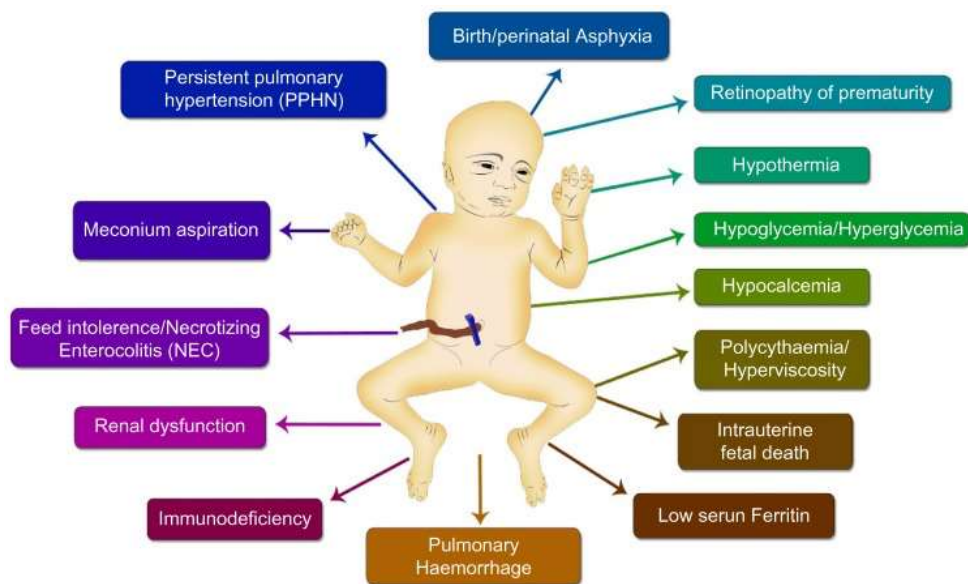
I. Preterm piglet

II. Low birth weight piglet – IUGR

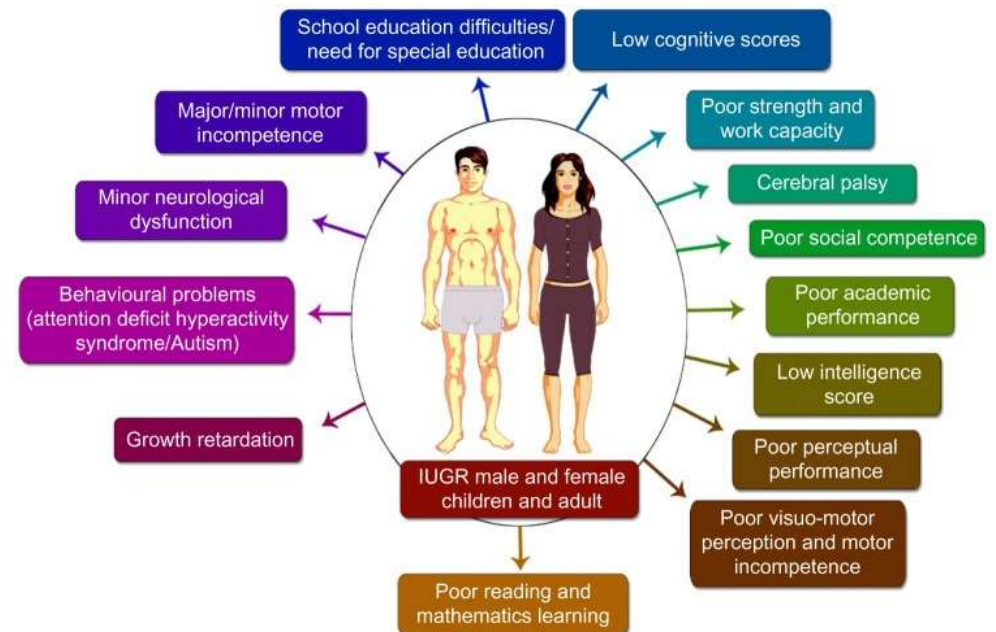
III. Neonatal – juvenile piglet

Low birth weight - IUGR

Short term effects

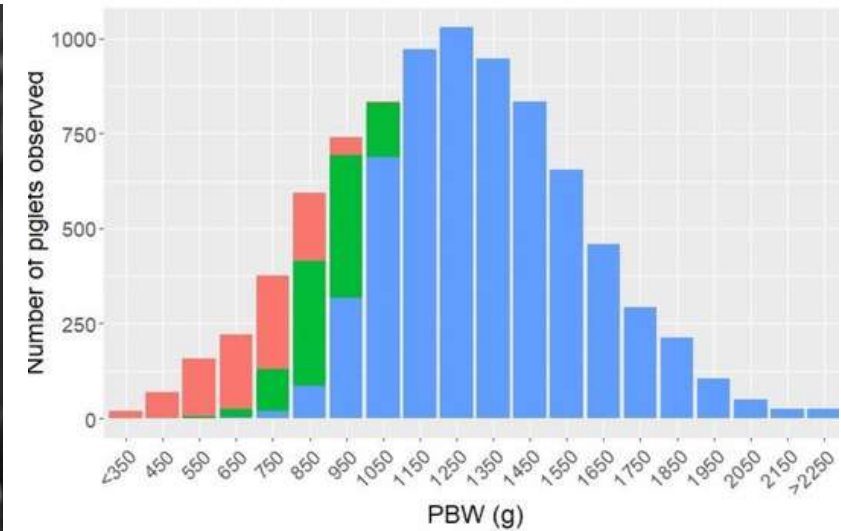


Long term effects



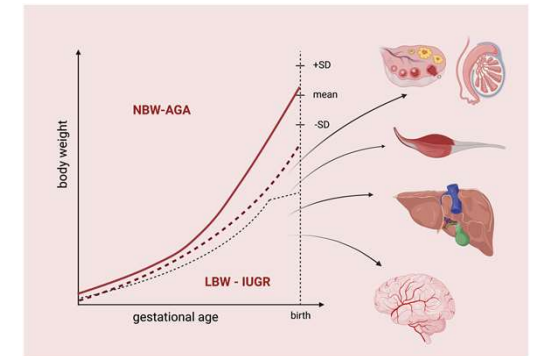
Low birth weight – IUGR piglet

- IUGR phenotype – brain sparing
- Low birth weight
- Natural occurrence – domestic hyper prolific sow – one health
 - Up till 20 % of a litter shows a low birth weight



Le
Lss neurons, reduced myelination,
neuroinflammation

Birth weight has no effect, IUGR not specifically tested



Reduced nephron number,
reduced glomerular filtration
rate, reduced glomerular
area



Altered structure, -omics, higher vulnerability
to oxidative stress

Regarding size a sparing effect
no IUGR related effects reported

Regarding size a sparing effect
no IUGR related effects reported

Content

0. Introduction

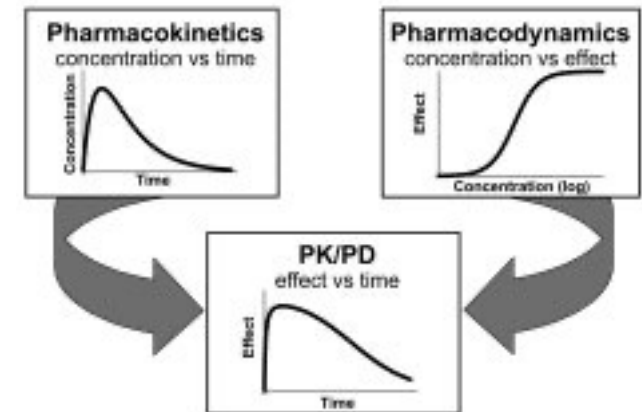
I. Preterm piglet

II. Low birth weight piglet – IUGR

III. Neonatal – juvenile piglet

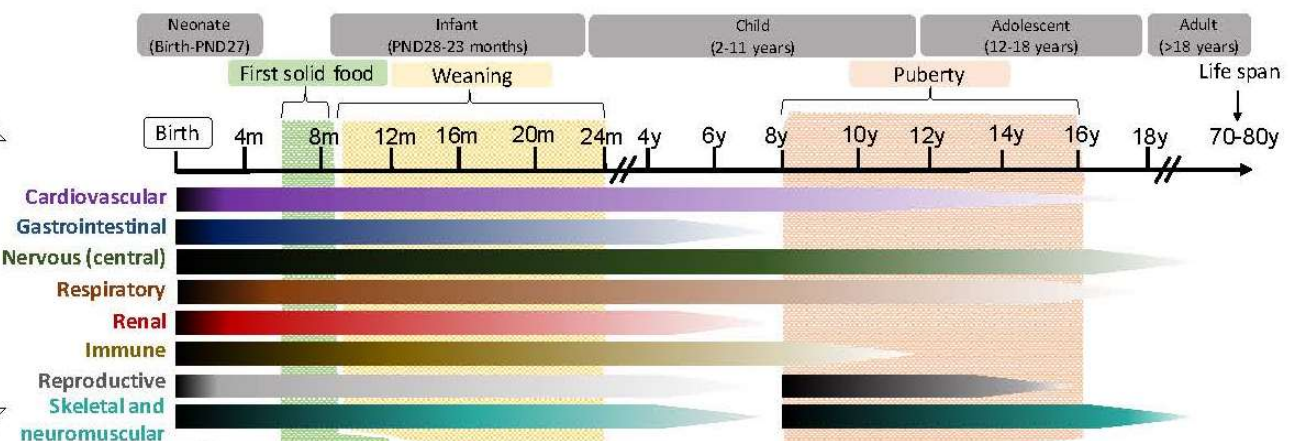
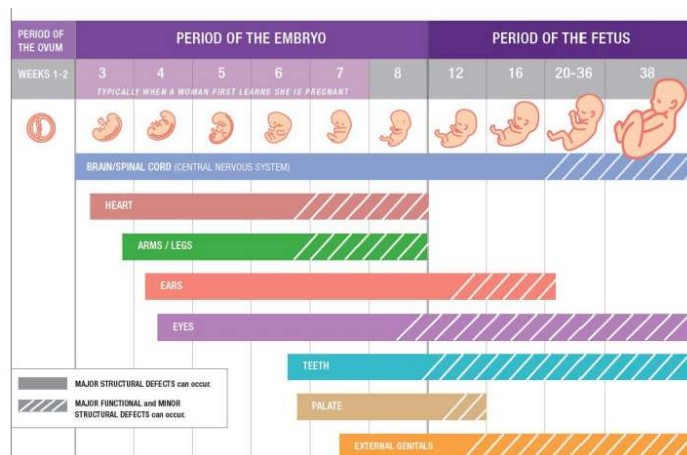
Neonatal up till juvenile – pharmacological research

- **Pharmacological research**
 - Pharmacokinetics (PK)
 - A(bsorption)D(istribution)M(etabolism)E(excretion)
 - In a body compartment (blood, CSF etc.)
 - Volume of distribution (of the compartment)
 - Clearance
 - Pharmacodynamics (PD)
 - Functionality of target organ (developmental stage, disease)



Neonatal up till juvenile – pharmacological research

- Pharmacokinetics (PK) - ADME
 - A(bsorption)D(istribution)M(etabolism)E(xcretion)
- Pharmacodynamics (PD)
 - Functionality of the target organ (effects but also side-effects)
- **Are both affected by developmental processes – need for pediatric PK/PD research/models**
 - Eg. Gastric emptying, gastric pH, drug-metabolizing enzymes (eg. in liver), drug transporters (eg. in intestine)



Neonatal up till juvenile piglets

- Minipig – micropig
- Routes of administration
- Immune function – rapid growth
- Background data (but is increasing)

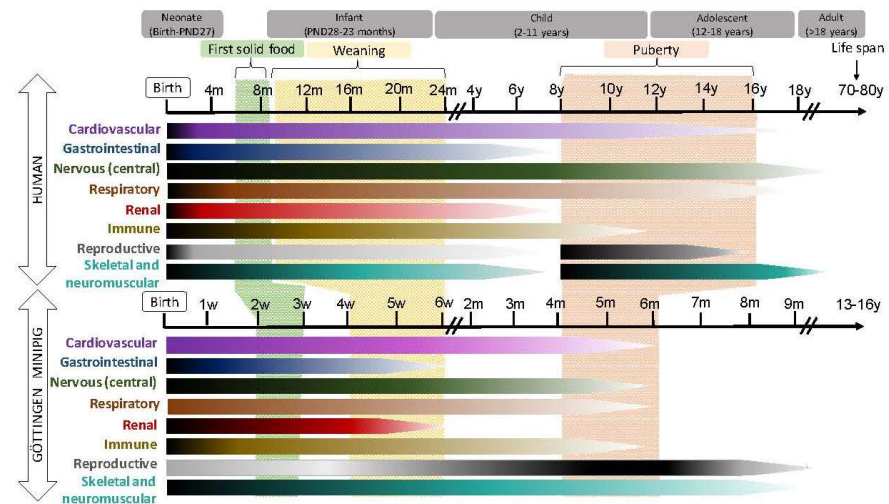
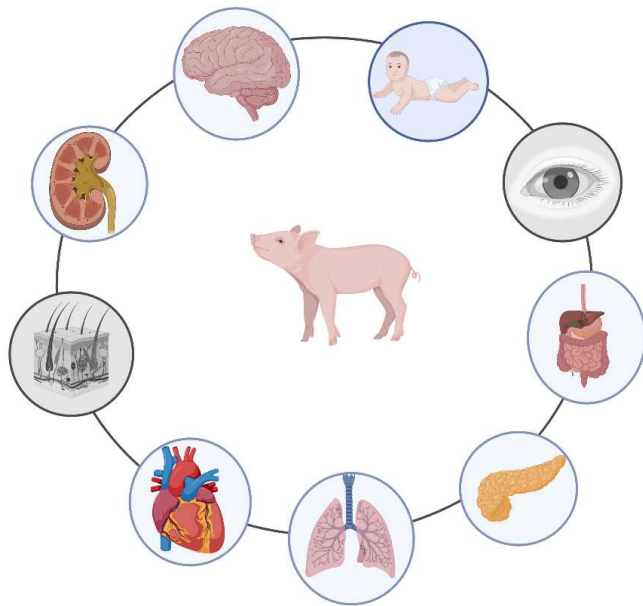


Figure 1. Schematic representation of the postnatal development of different organ systems in human (top) and Göttingen Minipig. In the horizontal bars, the intensity of the maturation process is represented by dark (more intense) and light (less intense) tones. The time bar represents weeks (w), months (m) or year (y) of life.

PK of ASOs in juvenile Göttingen Minipigs



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

Annmaria Braendli-Baiocco,^{1,2} Matthias Festag,^{1,2} Kamil Dumong Erichen,¹ Robert Persson,¹ Michael J. Mihatsch,² Niels Fisker,¹ Juergen Funk,¹ Susanne Mohr,¹ Rainer Constien,² Corinne Ploix,² Kevin Brady,² Marco Berrera,¹ Bernd Altmann,² Barbara Lenz,² Mudher Albassam,² Georg Schmitt,² Thomas Weiser,¹ Franz Schuler,² Thomas Singer,² and Yann Tessier¹



Gene expression profiling of key nucleases in the juvenile Göttingen minipig
Allan Paulo Valenzuela^{1,2}, Laura Buysens¹, Chloé Bars¹, Miriam Ayuso¹, Chris Van Ginneken¹, Neil Parrott², Yann Tessier², Georg Schmitt², Paul Barrow², Steven Van Cruichten¹

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.jeprotoc.2019.07.058>

No overt toxicity



Conclusion

- I. **Preterm piglet**
- II. **Low birth weight piglet – IUGR**
- III. **Neonatal – juvenile piglet**

- what are the potential harms for the (mini)pigs (in view of NHP or dogs)?
- can these harms be reduced more easily in (mini)pigs than in other species?
- are there potential benefits from the use of (mini)pigs relative to NHP and dogs?
- Decide on case-by-case what model is the best (predictive) and causes the least harm to the animal in question (no distinction can be made in view of species)



Thank you for your attention

Steven Van Cruchten, Charlotte vanden Hole, Falk Mielke, Marlotte Loyens,
Kevin Van Tichelen, Sara Prims, Lieselotte Van Bockstal, Gunther Vrolix,
Katty Huybrechts, Laura Buysens, Steve Van Bienst, Marina Stroe, Allan Vallenzuela

Collaborations: Ugent: Joris Michiels, Jeroen Degroot
Uantwerpen: Peter Aerts