Ontogeny of Phase I Metabolism of Drugs

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Disclosures

In the past 12 months, I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or providers of commercial services discussedin this presentation.

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Presentation Goals

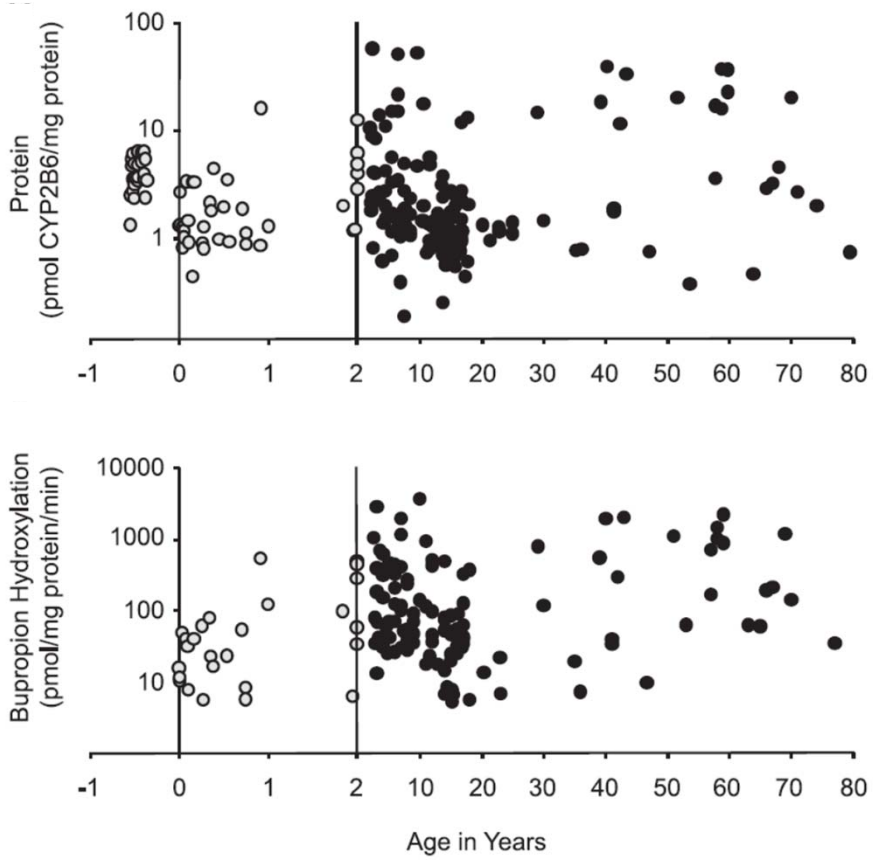
- Review the different sources of data contributing to current knowledge related to developmental trajectories of Phase 1 pathways
- Illustrate the challenges related to interpreting CYP ontogeny *in vivo* in the context of competing pathways
  - Indomethacin for treatment of PDA in the NICU (Tamorah Lewis, MD, PhD)
- Present new data regarding the ontogeny of scaling factors used to translate CYP developmental trajectories based on *in vitro* data to simulated drug disposition *in vivo*

Sources of “Ontogeny” Data: *In vitro*

- mRNA expression
  - qPCR
  - RNA-Seq (alternative splicing)
- Protein expression
  - Immunoblotting (antibody specificity; dynamic range)
  - Quantitative proteomics
- Catalytic activity (metabolite formation)
  - Specificity of probe substrates
  - Contribution of competing pathways

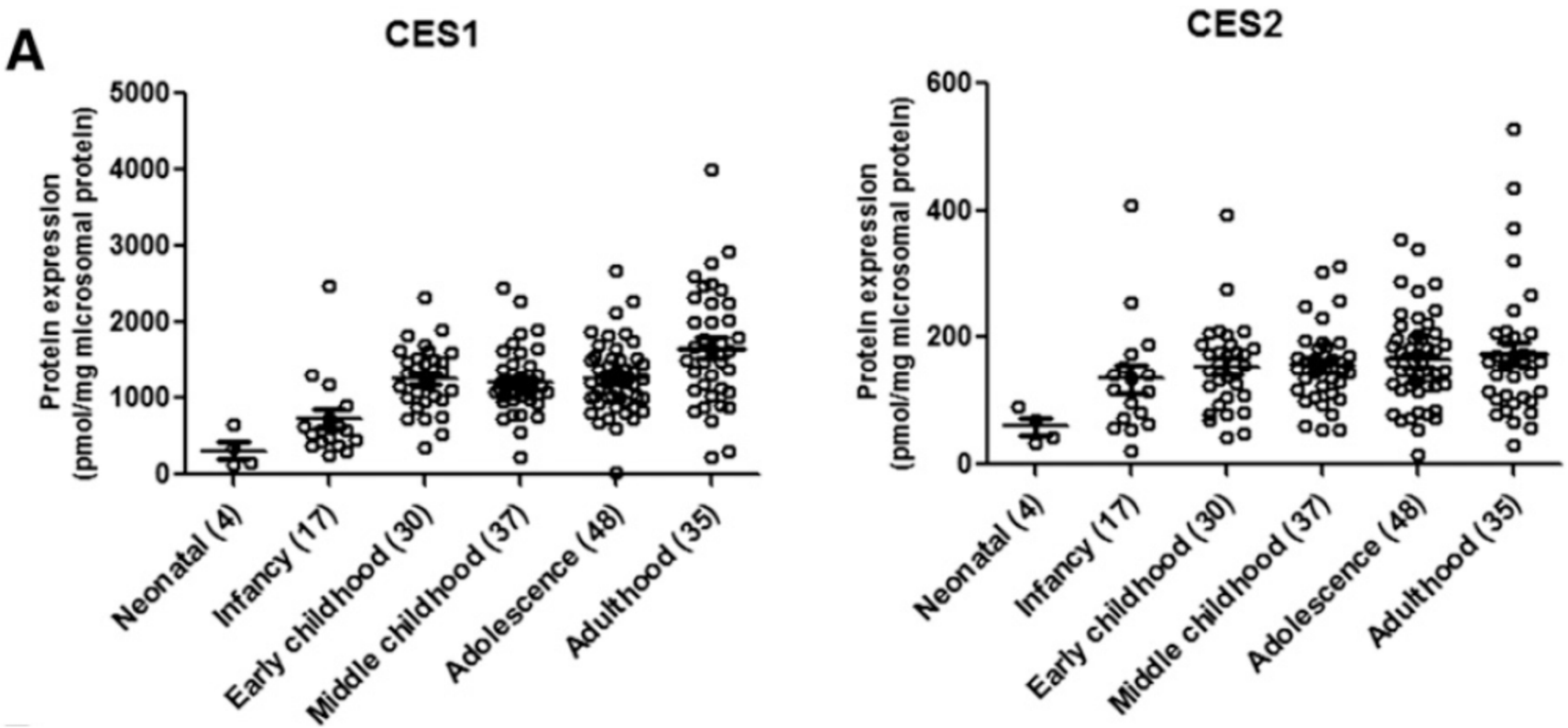
Ontogeny of CYP2B6

- Data analysis challenges related to tissue source and quality
- Immunoreactive protein detected in fetal liver, but no catalytic activity; no activity in 5 pediatric and 2 adult samples, and low (<LLOQ) in 21 pediatric and 2 adult
- Linear regression not appropriate
- Age-dependent break points by partitioning analysis
- No detectable genetic effect



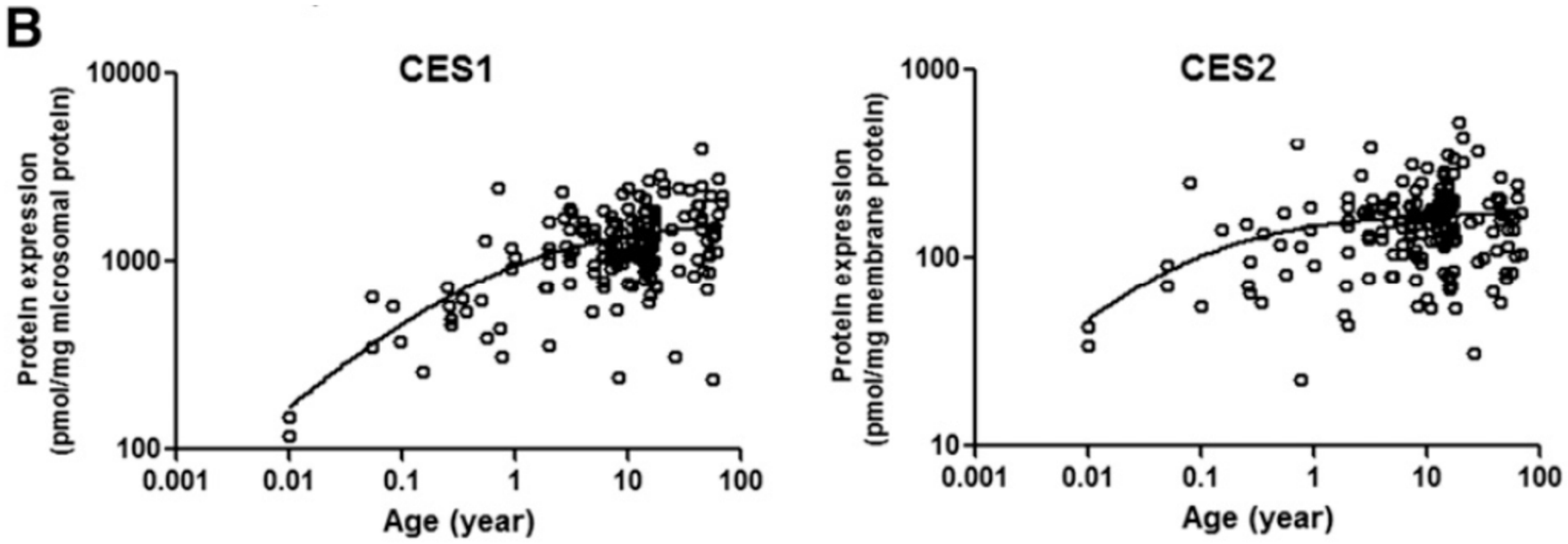
Pearce *et al,* DMD 2016;44:948-958

Ontogeny of CES1 and CES2



Boberg *et al,* DMD 2017;45:216-223

Ontogeny of CES1 and CES2



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Developmental Trajectory of CES1

- Data sparse at ages where developmental trajectory is steepest
- Linear regression not appropriate
- Microsomal and cytosolic expression for CES1 and CES2

Ontogeny equation[a]	$F = \left(\frac{Adult_{max} - F_{birth}}{Age50^n + Age^n}\right) \times Age^n + F_{birth}$
CES1 ontogeny parameters[b]	F_{birth}, $Adult_{max}$, Age_{50}, and n: 0.20, 1, 1.10, and 0.56, respectively[b]

[a]Equation terms: $Adult_{max}$, maximum average relative protein abundance; Age, age in years of the subject at the time of sample collection; Age50, age in years at which half-maximum adult protein abundance is obtained; F, fractional protein abundance in adult samples; F_{birth}, fractional protein abundance (of adult) at birth; n, exponential factor.

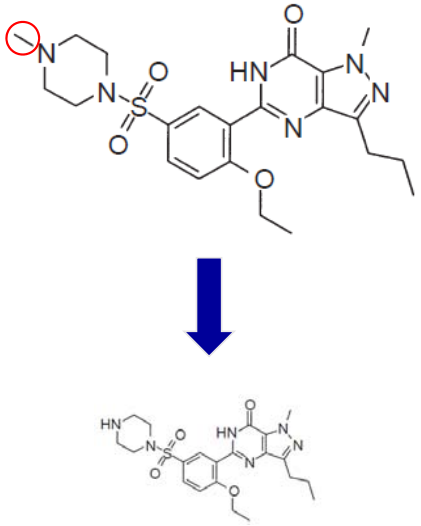
[b]Since CES1 is functionally active in both microsomal and cytosolic fractions, the ontogeny equation was derived based on the total microsomal plus cytosolic abundance of CES1 per gram of liver tissue. To do so, reported values of milligram of microsomal and cytosolic proteins per gram liver tissue (39.8 and 80.7 mg/ml, respectively) were used to first obtain microsomal and cytosolic CES1 abundance per gram of liver tissue. Then, the total microsomal plus cytosolic abundance of CES1 per gram of liver tissue was derived by adding the two values. Finally, the adult normalized fractional values were derived by considering $Adult_{max}$ to be equal to 1.

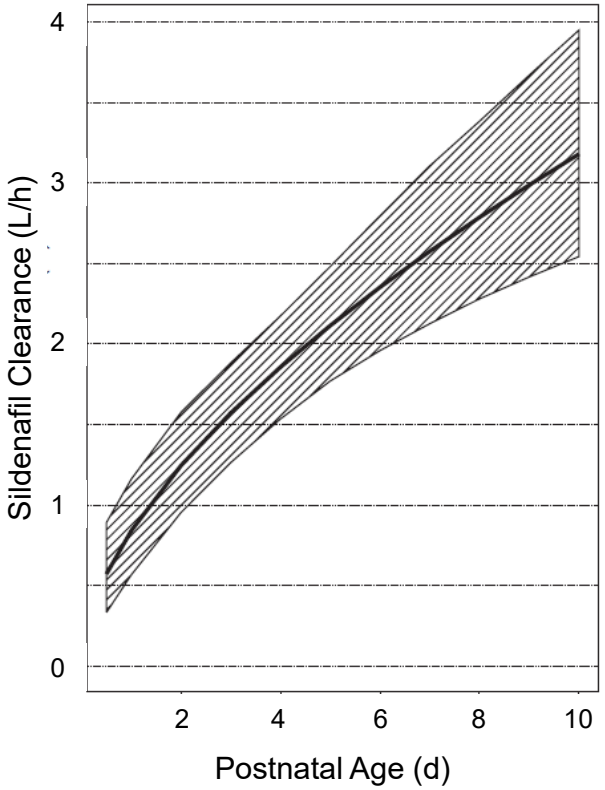
Sources of "Ontogeny" Data: *In vivo*

- Pharmacokinetic studies of model substrates:
  - Disappearance (clearance) of parent drug/probe substrate
  - Challenge: multiple metabolites, different pathways
    - *e.g.,* atomoxetine
    - Formation of pathway-specific metabolite most relevant
  - Challenge: IV *vs* oral administration
    - Gut *vs* hepatic metabolite formation
  - Challenge: Plasma or urinary metabolite data?
    - To assess ontogeny, plasma metabolite AUC data must be formation rate-limited; urine data allow estimate of fractional contribution of pathway
  - Cross-sectional *vs* longitudinal data

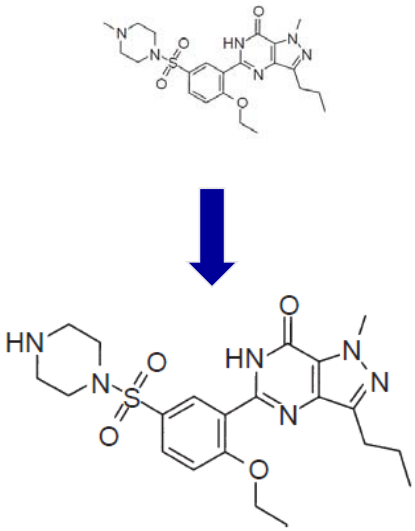
Ontogeny of Sildenafil Disposition in Neonates: (Hepatic CYP3A)

Day 1:
Clearance = 0.84 L/h or 8.05 L/h/70 kg
(*N*-desmethyl metabolite predicted to be11% of parent)





Day 7:
Clearance = 2.58 L/h or 24.7 L/h/70 kg
(*N*-desmethyl metabolite predicted to be 71% of parent)

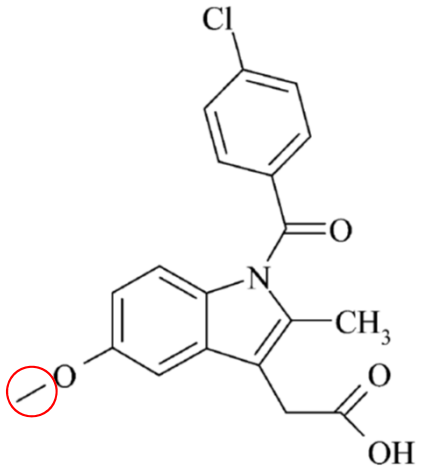


Role for CYP2C9?

Mukherjee *et al*. Clin Pharmacol Ther 2009;85:56-63

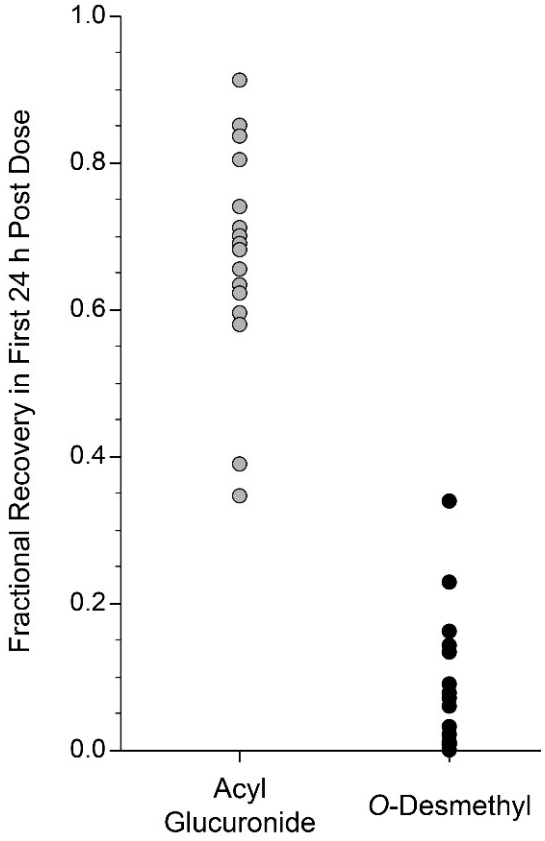
Cross-Sectional *vs* Longitudinal Studies:
Indomethacin in Patent Ductus Arteriosus

O-demethylation
(ODM)



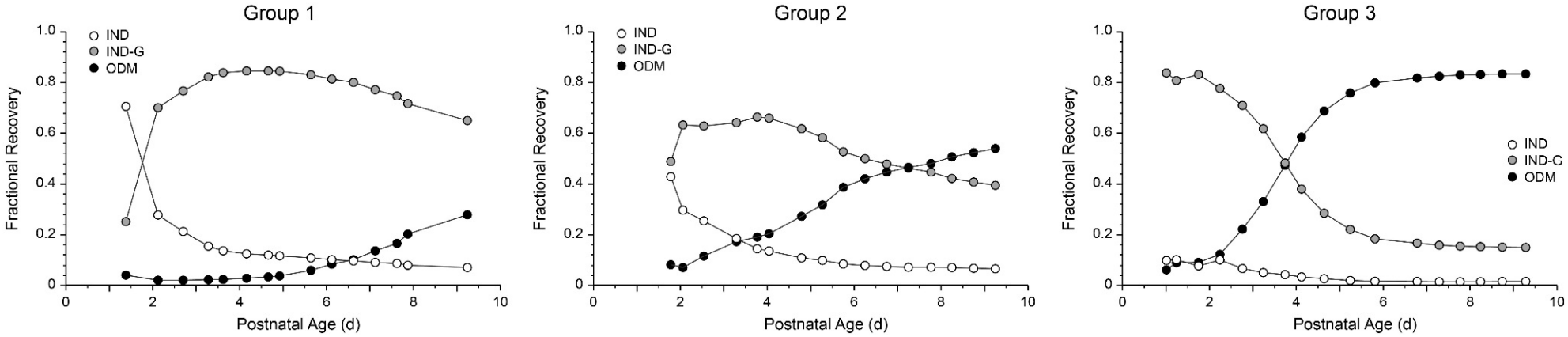
Indomethacin

Acylglucuronidation
(IND-G)



Lewis TR *et al Pediatr Res* 2018; 84:325-327

CYP Ontogeny… Which Developmental Trajectory?



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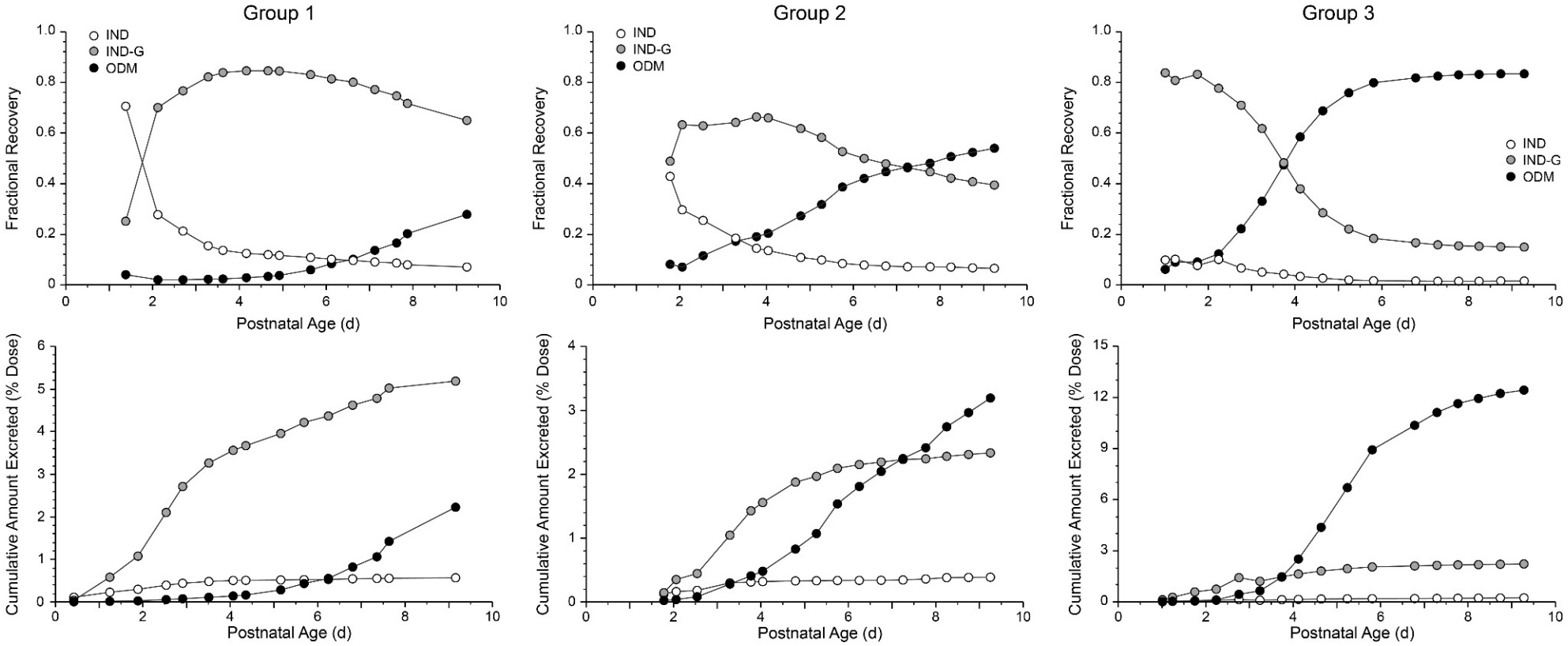

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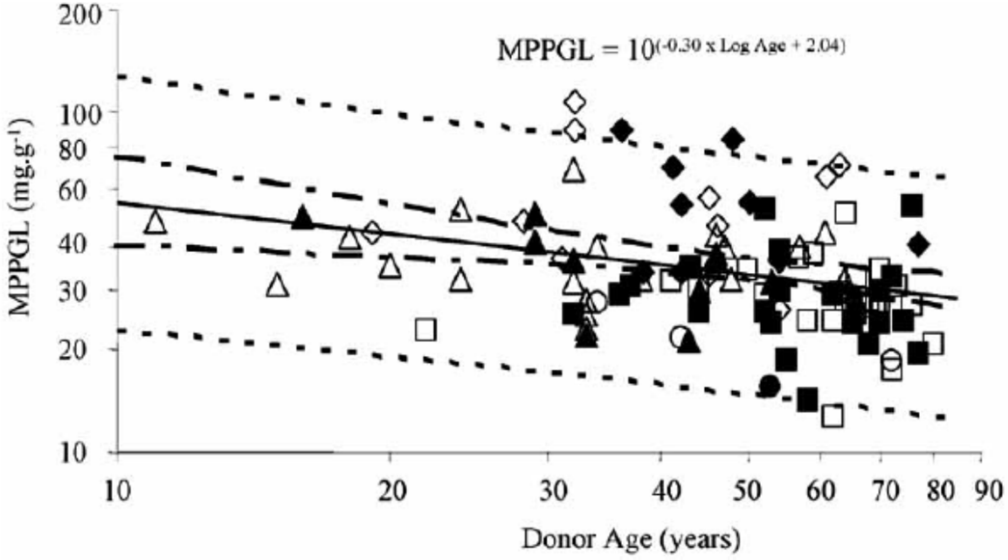
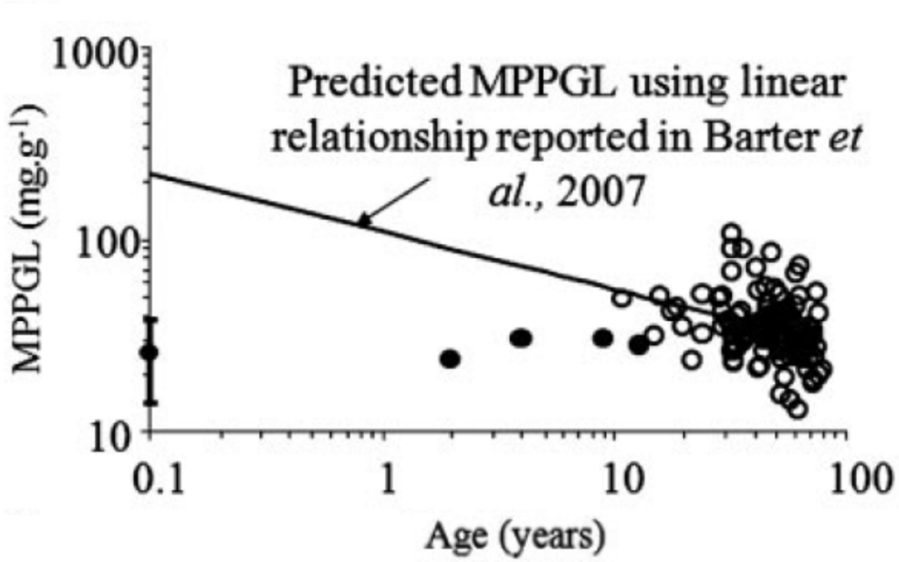
Ontogeny of Scaling Factors: MPPGL



Barter *et al,* Curr Drug Metab 2007; 8:33-41



Barter *et al,* DMD 2008; 36:2405-2409

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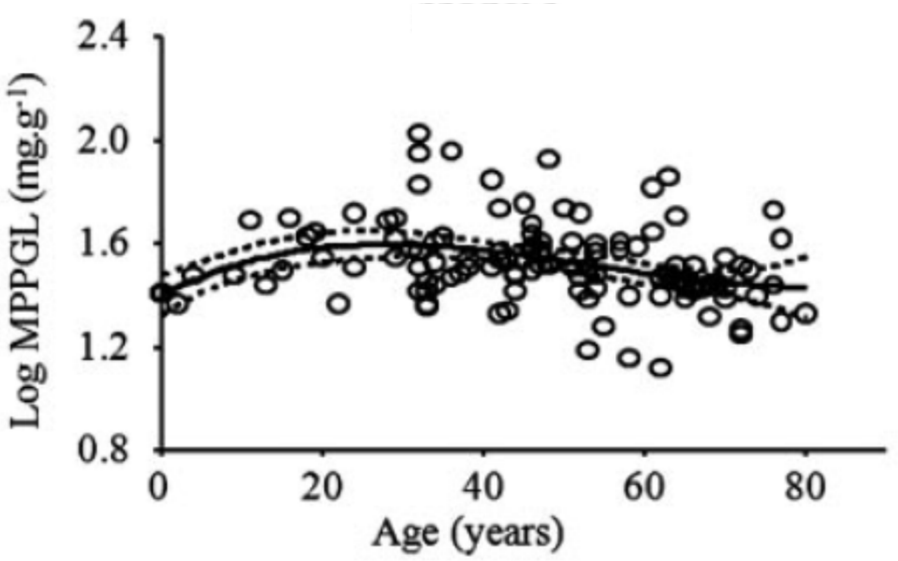
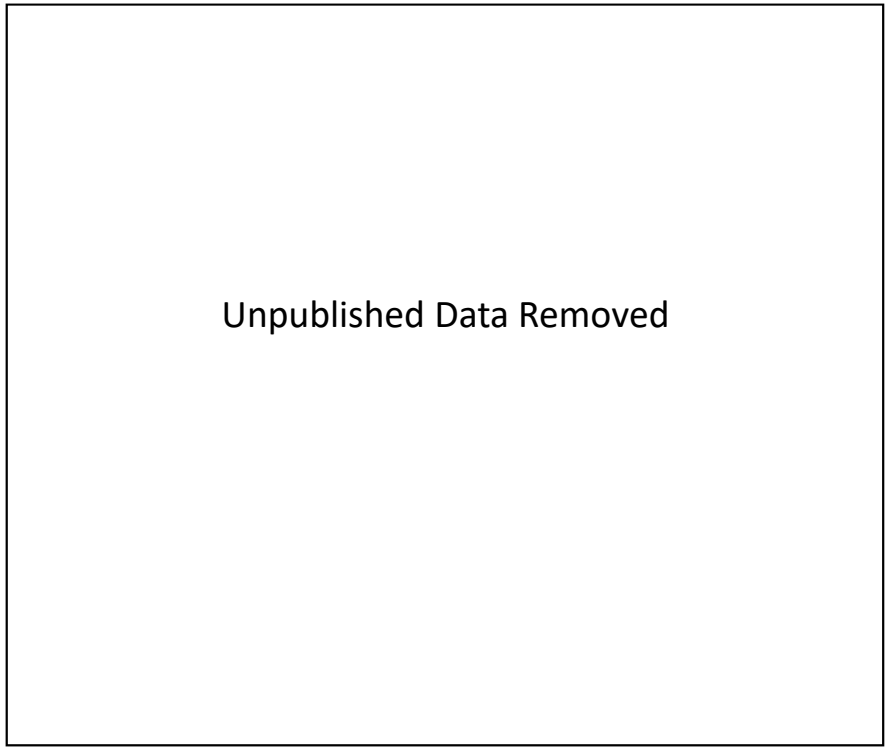


MPPGL= $10^{1.434+0.008xAge-0.00038xAge^2+0.000024xAge^3}$

Unpublished Data Removed

Barter *et al,* DMD 2008; 36:2405-2409

Ontogeny of Scaling Factors: MPPGL

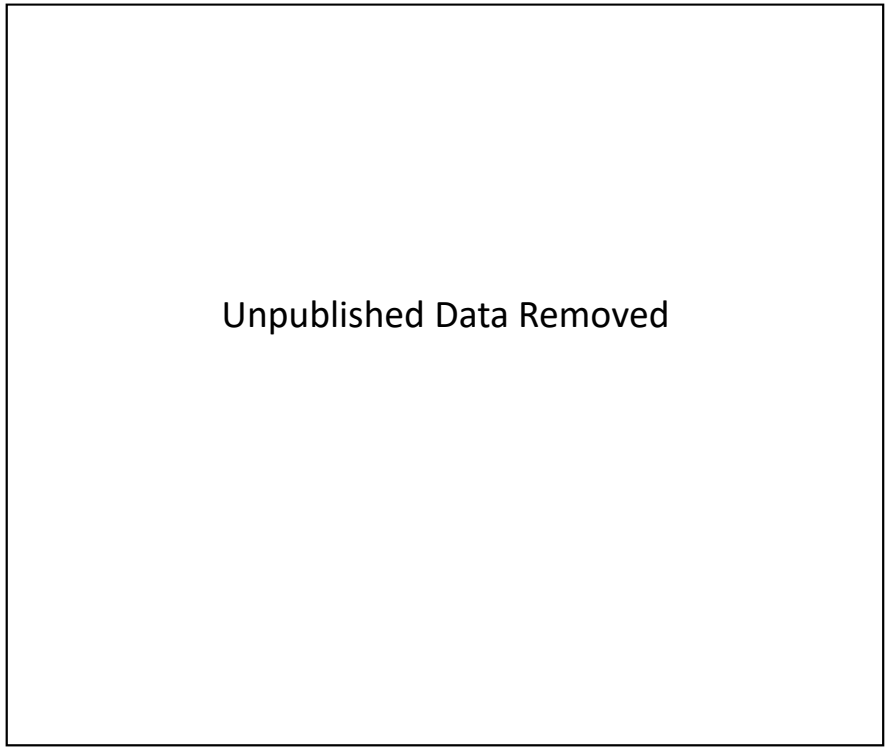


Group	NICHD Age Range		
0	Fetal		n = 5
1	Infancy	(28 d-12 m)	n = 20
2	Toddler	(13 m-2 y)	n = 9
3	Early Child	(2y-5y)	n = 21
4	Middle	(6y-11y)	n = 32
5	Early Adol	(12y-18y)	n = 47
6	Adult_1	(19y-50y)	n = 16
7	Adult_2	(>50y)	n = 15

Manuscript in preparation

Williams *et al*, Pediatrics 2012; 129:S153-S160

If Most CYPs Have A Similar Developmental Trajectory, What is the Ontogeny of Total CYP Content?



Group	NICHD Age Range		
0	Fetal		n = 1
1	Neonate	(Birth-27 d)	n = 4
2	Infancy	(28 d-12 m)	n = 18
3	Toddler	(13 m-2 y)	n = 9
4	Early Child	(2y-5y)	n = 21
5	Middle	(6y-11y)	n = 40
6	Early Adol	(12y-18y)	n = 47
7	Adult_1	(19y-50y)	n = 33
8	Adult_2	(>50y)	n = 19

Manuscript in preparation

Williams *et al*, Pediatrics 2012; 129:S153-S160

Ontogeny of Total Hepatic CYP Content

Summary and Challenges

- For an individual drug, impact of “ontogeny” on clearance is greatest when PGx contribution$\rightarrow$0, and fraction metabolized$\rightarrow$1
- Quantitative proteomic data may allow refinement of equations describing developmental trajectories
- Developmental trajectories derived from *in vivo* data may more informative for predictive modeling and simulation
- Experience with one CYP substrate is not directly applicable to other substrates for same pathway (Calvier *et al* CPT-PSP 2018: 7:174-185)
  - Consider ontogeny and genetic variation for all ancillary/competing pathways

Summary and Challenges

- Cross-sectional data probably sufficient for “population” purposes
  - Data generally are sparse for periods where the velocity of change is greatest
  - Extensive inter-individual variability obscures developmental changes that may be occurring during critical periods of change, such as around puberty
- Longitudinal data more informative at the level of individual patients
  - Detecting patterns that may not be apparent from cross-sectional data
  - Potential implications for systemic exposure and clinical response
  - Data capture needs to be sufficiently long to observe developmental changes
- Challenge: Collecting the data