Extrapolation in Pediatric Drug Development: *Dealing with Uncertainty in Extrapolation Assumptions*

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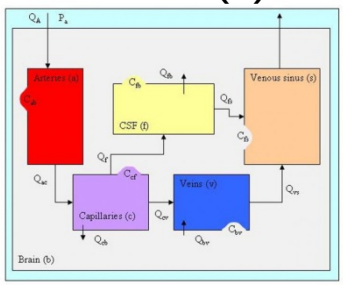
Uncertainty in Extrapolation Assumptions

Degree of Difficulty/Uncertainty

- Disease Progression/ Physiology
- Response to prior interventions
- Expected PD response to investigational drug
- Expected investigational drug PK

Model(s)



$$Ci = \frac{\left(\frac{Ceo\,Kc}{Vi} + \frac{Cio\,(Kc+Kd+Kr)}{Ve} - \frac{G\,Kc}{Ve\,Vi\,b} - Cio\,b\right)e^{(-b\,t)}}{a-b} - \frac{\left(\frac{Ceo\,Kc}{Vi} + \frac{Cio\,(Kc+Kd+Kr)}{Ve} - \frac{G\,Kc}{Ve\,Vi\,a} - Cio\,a\right)e^{(-a\,t)}}{a-b} + \frac{G\,Kc}{Ve\,Vi\,a\,b}$$

Assumptions can be stated quantitatively and integrated in a modeling framework

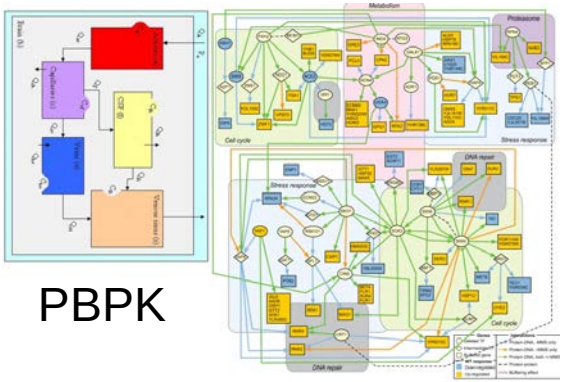
Model(s) can be used to design pediatric studies to validate quantitative assumptions

Pediatric Investigation

- ✓Dose selection
- ✓Biomarker selection
- ✓Sample size
- ✓Power
- ✓Inclusion/exclusion criteria

Evaluation of Different Modeling Approaches for Extrapolation

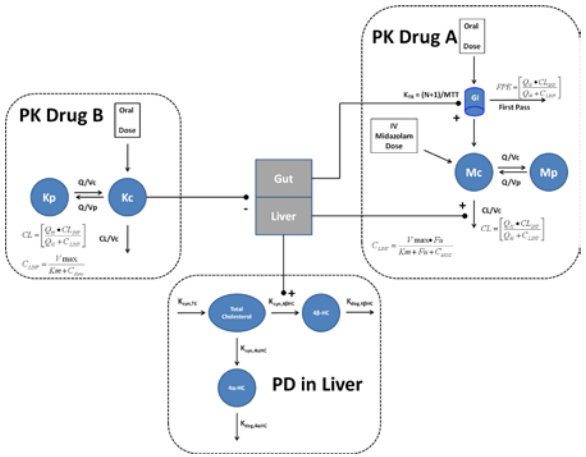
Physiological/Mechanism Based Model



PBPK

- Mathematical functions for biological relationships of system
- Disease biology & progression
- Drug PK, binding and potency
- Multiple scales of time and space
- Inter-subject variability defined by structure of model
- Useful for extrapolation

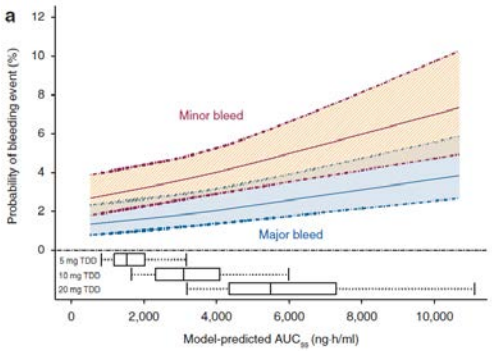
Semi-Physiological/Mechanism Based Model



- Simplify the system to key processes
- Usually a single scale of time
- Maybe multiple scales of space
- Only include key processes needed for extrapolation
- Inter-subject variability can be estimated as a random effect
- May be useful for extrapolation

Empirical Model

$$\lambda_i = \alpha_0 + \beta_1 \times AUC_{ss,i} + \beta_{cov} \times COV$$



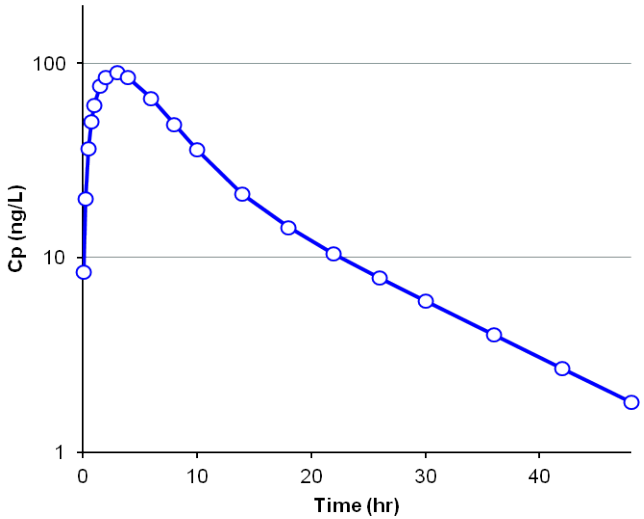
- Describe data accurately
- Few obvious assumptions
- Statistical rigor is key element
- Estimate level of variability accurately
- Only useful for interpolation

Extrapolation of PK/PD: Hypothetical Enzyme Inhibitor

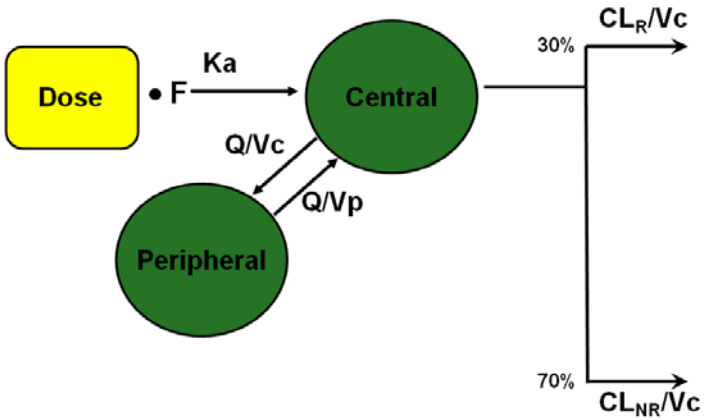
- Drug Z is an oral hypothetical competitive inhibitor of an enzyme involved in a disease that affects adults and children
  - Disease physiology and progression appear to differ between children and adults
  - Based on non-clinical data and adult clinical studies, the therapeutic goal is to raise the levels of the product of this enzyme by 20-fold
- Pharmacokinetics: based on adult studies, Drug Z is eliminated 30% by kidney and 70% by metabolism in liver
  - CYP3A4, CYP1A2, and CYP2C9 contribute to 99% of metabolism
- Pharmacodynamics: the biomarker of this enzyme's inhibition can be measured in plasma
  - Expression level and production rate of the enzyme have been shown to change with age

Extrapolation of PK: Semi-Physiological Model

Drug Z Concentration vs. Time



2-Compartment PK Model with Separation of Renal and Non-Renal Clearance

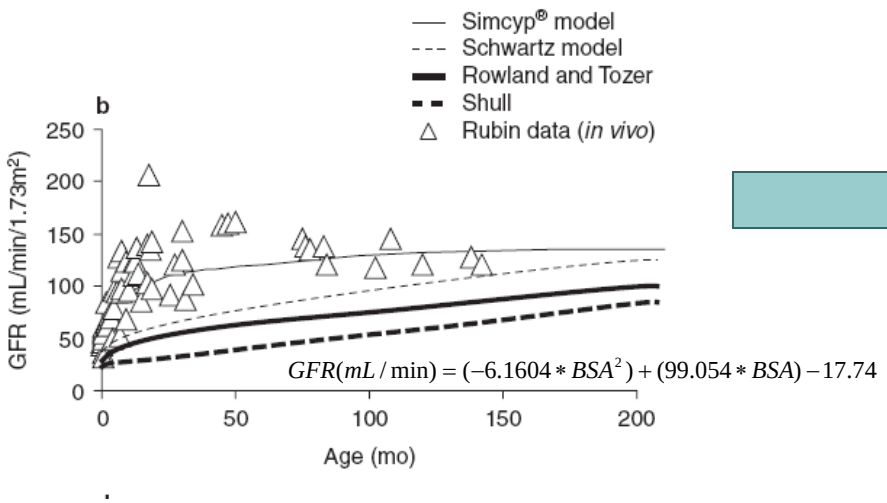


- Model parameters can be interpreted physiologically
  - Simplifications have been made regarding some mechanisms of ADME
- Assumptions can be made about how parameters will change to predict PK in pediatric subjects

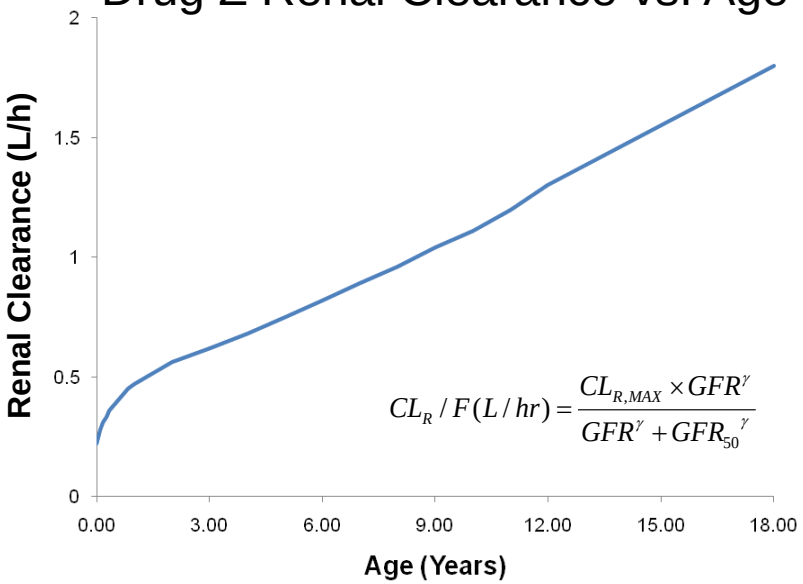
Extrapolation of PK: Renal Clearance

- Renal clearance of drugs is dependent on GFR
  - Quantitative relationship between body size and GFR has been established
- Apply this knowledge to model of renal clearance of drug Z in adult
  - Predict renal clearance as a function of age/GFR

GFR vs. Age*



Drug Z Renal Clearance vs. Age



*Johnson, TN, Rostami-Hodjegan, A, and Tucker, GT. Clinical Pharmacokinetics 2006; 45(9): 931-956.

Extrapolation of PK: Hepatic Clearance

- Drug Z is metabolized in the liver
  - 76% CYP3A4
  - 16% CYP1A2
  - 6% CYP2C9
- Maturation of these pathways has been reported*

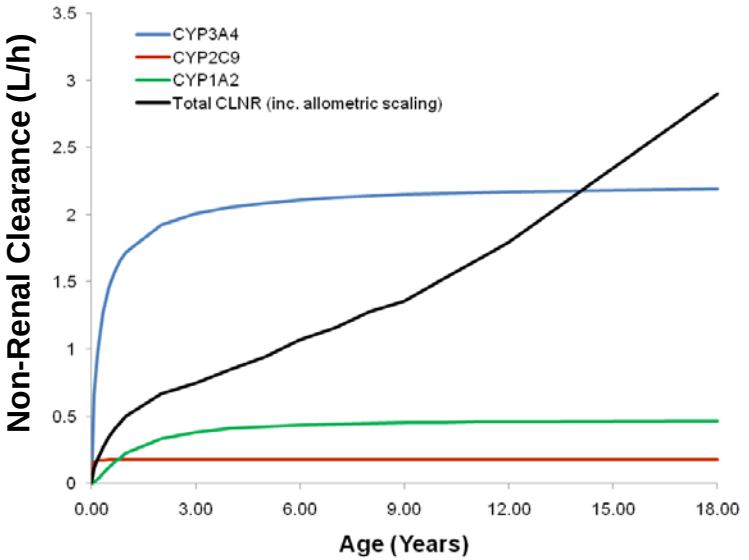
Enzyme Maturation Functions

$$CL_{NR,3A4} = \frac{CL_{NR,Adult} \times 0.76 \times Age^{0.83}}{0.31 \times Age^{0.83}}$$

$$CL_{NR,1A2} = \frac{CL_{NR,Adult} \times 0.16 \times Age^{1.41}}{1.13 + Age^{1.41}}$$

$$CL_{NR,2C9} = \left(CL_{NR,Adult} \times 0.06\right) \times \left[\frac{0.79 \times Age}{0.01 + Age} + 0.21\right]$$

Drug Z Hepatic Clearance vs. Age

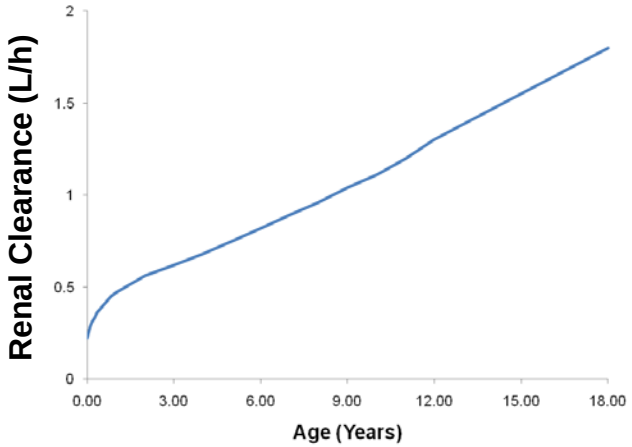


*Johnson, TN, Rostami-Hodjegan, A, and Tucker, GT. Clinical Pharmacokinetics 2006; 45(9): 931-956.

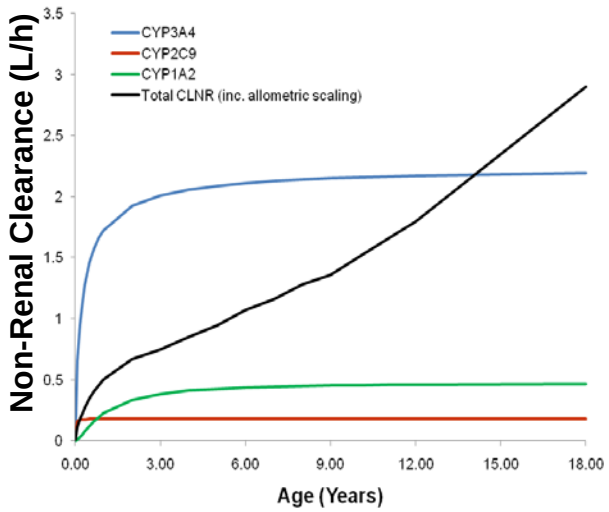
Bristol-Myers Squibb

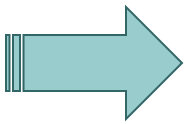
Extrapolation of PK: Combining Renal and Hepatic Clearance to Predict Exposure

Drug Z Renal Clearance vs. Age

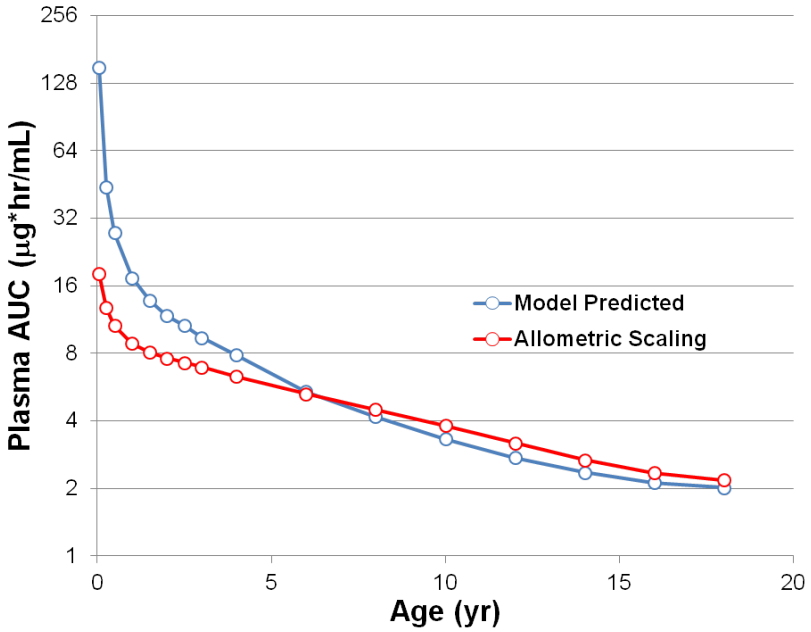


Drug Z Hepatic Clearance vs. Age





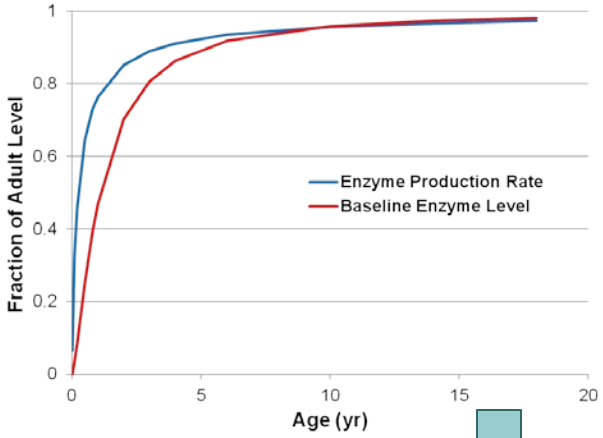
Exposure vs. Age for 10 mg Dose of Drug Z



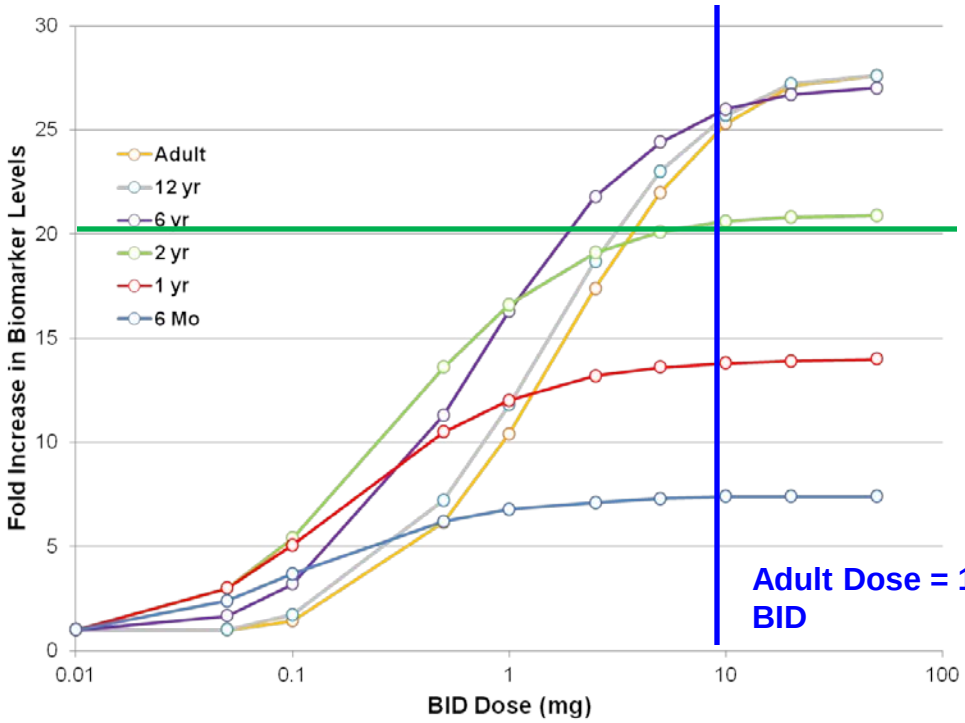
- Exposure increases dramatically in younger subjects
- Allometric scaling inaccurate in subjects younger than 6 years

Extrapolation of PK and PD: Effect of Age on PD Response

Maturation of Target Enzyme and Production Rate



Effect of Age on Drug Z Dose-Response



- Shape of D-R curve changes with age
- Younger children have a much lower maximum PD response
  - Despite much higher drug exposures
- What effect will this have on clinical endpoint?

Extrapolation Beyond PK and PD

Current: extrapolation of drug PK (and possibly PD)

- Gaining wider acceptance in industry, academia and regulatory agencies

Future: need to go beyond PK/PD for evaluation of the more challenging assumptions in extrapolation of efficacy

- Similarity of disease/disease progression
  - Models that incorporate disease mechanisms may be used to evaluate assumed differences in disease physiology between adult and pediatric
- Similarity of response to intervention
  - Drug MoA's may be incorporated into disease models to evaluate the mechanism(s) of assumed differences in drug pharmacology

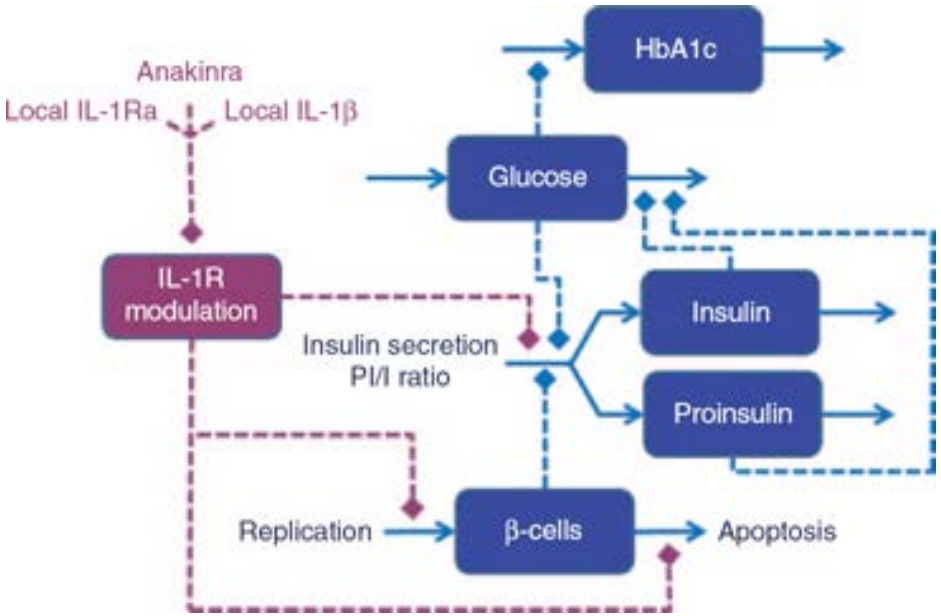
Quantitative Systems Pharmacology (QSP) Models Can Facilitate Extrapolation

Numerous QSP models have been developed to support drug development in adult disease

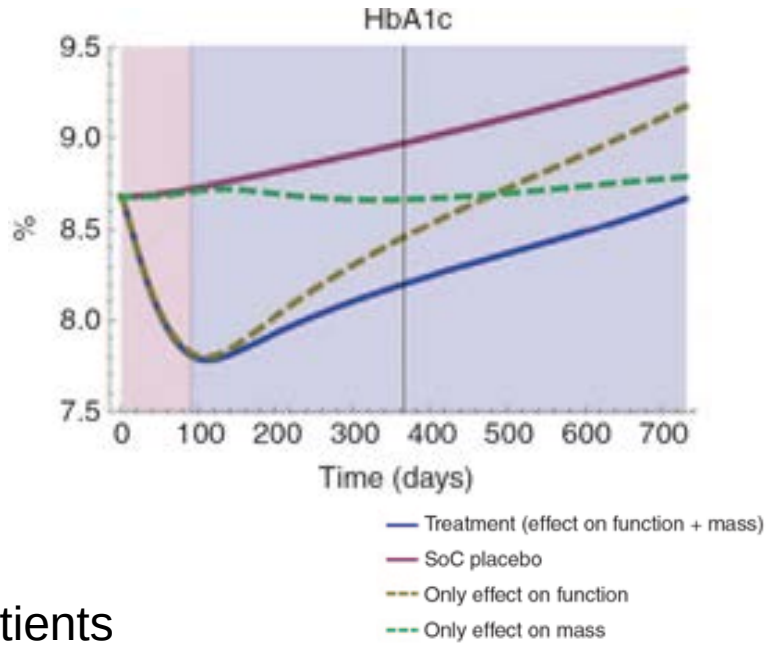
- Diabetes
  - **T2DM:** *Ermakov et al. Frontiers in Pharmacology 2014 Oct 22; 5:232*
  - **T1DM:** *Schaller et al. CPT: Pharmacometrics & Systems Pharmacology 2013 Aug 14;2:e65*
- Rheumatoid Arthritis
  - **Adult RA:** *Schmidt et al. BMC Bioinformatics. 2013 Jul 10;14:221*
- Asthma
  - **Leukotriene System:** Demin at al. CPT: *Pharmacometrics & Systems Pharmacology* 2013 Sep 11;2:e74
- Osteoporosis
  - **Bone Mineral Density:** Peterson & Riggs: CPT: *Pharmacometrics & Systems Pharmacology* 2012 Nov 14;1:e14
- Cancer
  - **Lymphoma:** *Shah et al. Journal of Pharmacokinetics and Pharmacodynamics 2012 Dec;39(6):643-59*
  - **Angiogenesis:** *Sharan and Woo. CPT: Pharmacometrics & Systems Pharmacology 2014 Oct 8;3:e139*
  - **Pancreatic Cancer:** *Eissing et al. Frontiers in Physiology 2011 Feb 24;2:4.*
- Schizophrenia
  - **Negative Symptoms:** *Spiros et al. Frontiers in Pharmacology 2014 Oct 21;5:229.*
- Alzheimer's Disease
  - **Cognitive Deficit:** *Roberts at al. Alzheimer's Research & Therapy 2012 Nov 26;4(6):50*
- Coagulation
  - *Siegmund at al. British Journal of Clinical Pharmacology 2014 Dec 16*

Extrapolation of Efficacy using a QSP Disease Model for T2DM

High Level Model Diagram



Predicted Disease Progression and Treatment Effects (Anti-IL1-β



Example of assumptions for pediatric T2DM patients

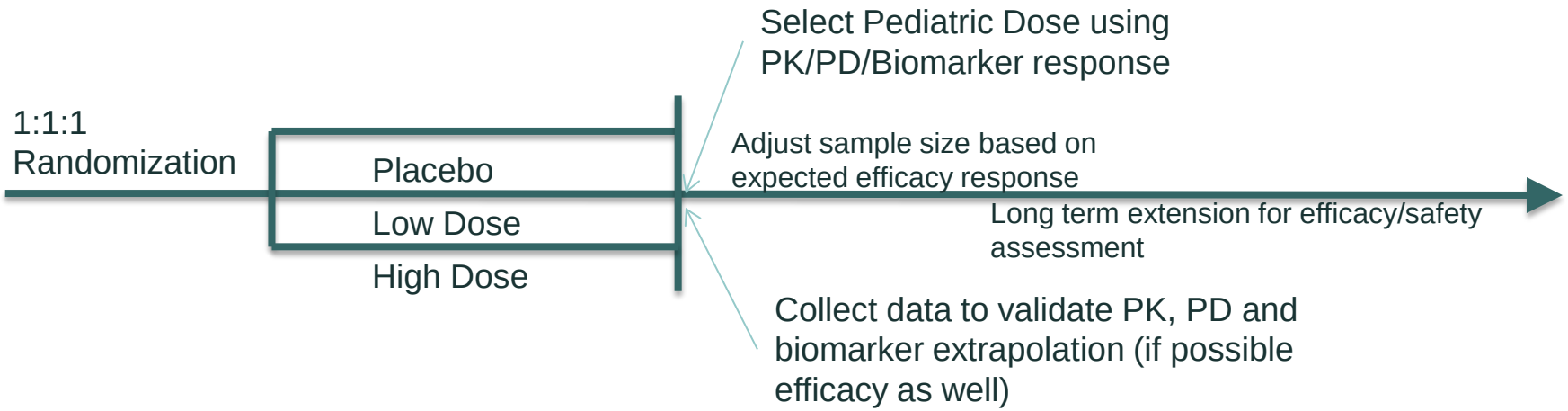
- Improved β-cell mass and function
- Greater insulin sensitivity in peripheral tissues
- More rapid decline in β-cell function

*Palmer, R et al. CPT Pharmacometrics Syst Pharmacol. 2014 Jun 11;3:e118.

Validation of Extrapolation in Pediatric Development Program

- Ability to extrapolate PK, PD, biomarker and clinical efficacy in pediatric subjects permits a more rational and efficient design to the pediatric clinical development program
- Sample size can be determined based on predicted PK, PD, biomarker and/or efficacy response
- Account for practical considerations for particular pediatric population

Adaptive Design to Validate Extrapolation



Conclusions

- Mechanism-based models can be used to evaluate the assumptions in extrapolation of PK, PD, disease and disease progression
  - PK and PD are more common and straightforward
  - Mechanism-based QSP disease models can be used to extrapolate disease physiology and predict clinical response
- Numerous QSP models have been developed to characterize disease in adults
  - Can be adapted to incorporate assumptions of differences in disease physiology/progression between pediatric and adult
- Validation Strategy
  - Pediatric development plan can be designed to validate the extrapolation assumptions and model predictions for PK, PD, biomarker and clinical efficacy