

# Developmental Pharmacodynamics: An Overview

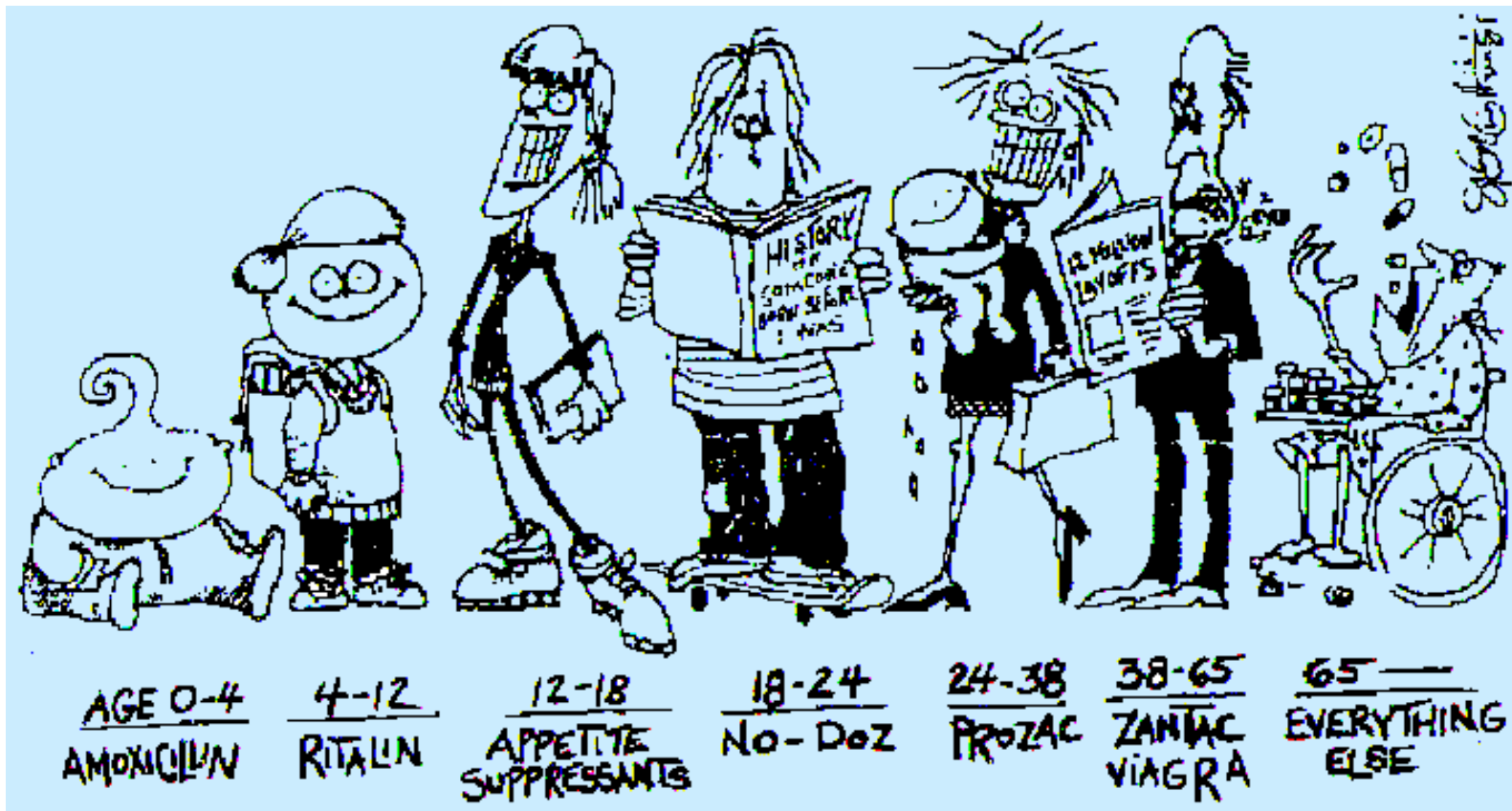
**Gregory L. Kearns, PharmD, PhD, FCP, FAAP**

Past President, Arkansas Children's Research Institute

Ross and Mary Whipple Family Distinguished Research Scientist

Professor Emeritus of Pediatrics, University of Arkansas

# Introduction to Developmental Pharmacology...



**Supplement Article**

**The Journal of Clinical Pharmacology 2018, 58(S10) S10–S25©2018,  
The American College of Clinical Pharmacology DOI: 10.1002/jcph.1284**

# **Developmental Changes in Pharmacokinetics and Pharmacodynamics**

**John van den Anker, MD, PhD, FCP<sub>1,2,3</sub>, Michael D. Reed, PharmD, FCCP, FCP<sub>4</sub>,  
Karel Allegaert, MD, PhD<sub>3,5,6</sub>, and Gregory L. Kearns, PharmD, PhD, FCP**



**DOSE**



**CONCENTRATION**



**EFFECT**

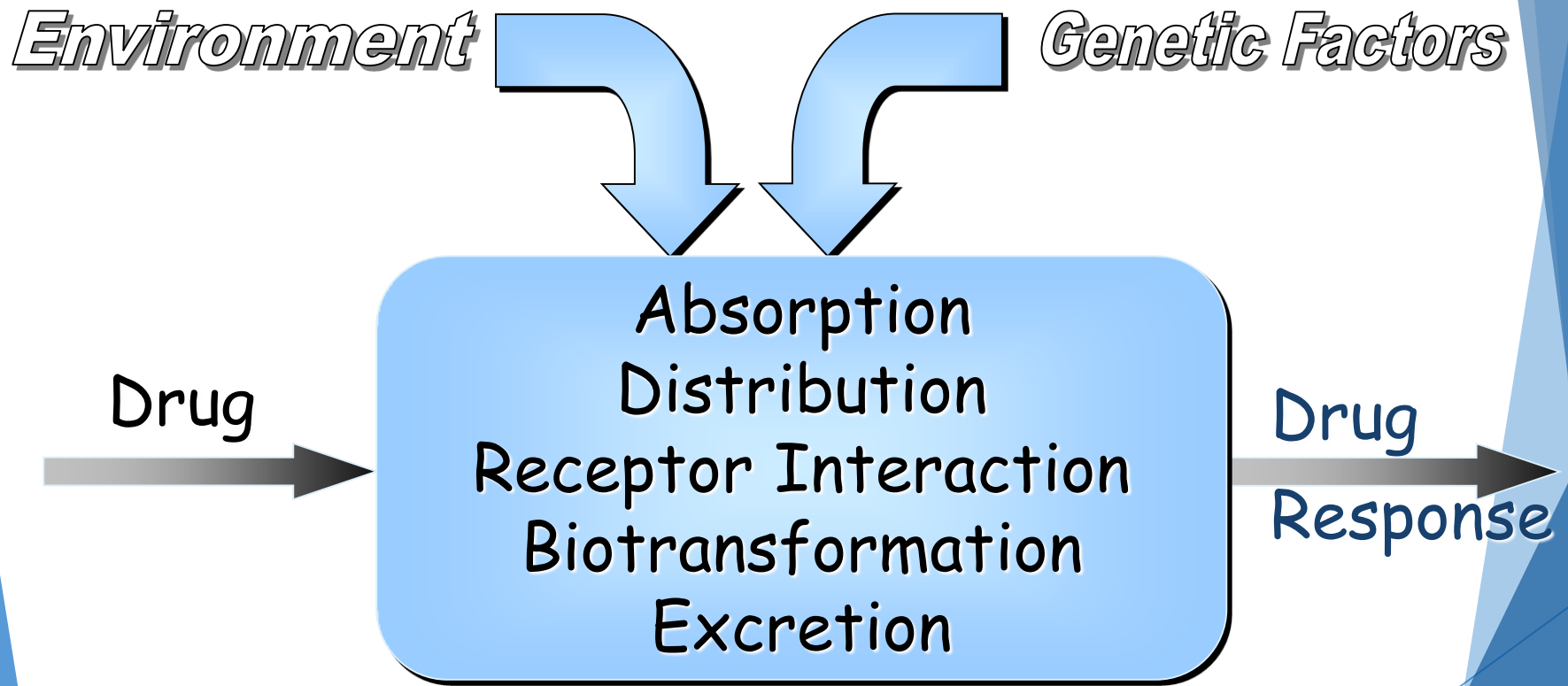


**EFFICACY**



**TREATMENT  
OUTCOME**

# Variation in Drug Response



## Understanding Developmental Pharmacodynamics Importance for Drug Development and Clinical Practice

*Hussain Mulla*

Centre for Therapeutic Evaluation of Drugs in Children, University Hospitals of Leicester, Leicester, UK

“the study of age-related maturation of the structure and activity of biologic systems and their effects on response of children to pharmacotherapy”





TERRACOTTA

INDOOR BABIES

\$7.95

QUALITY GUARANTEED

MADE IN ITALY

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

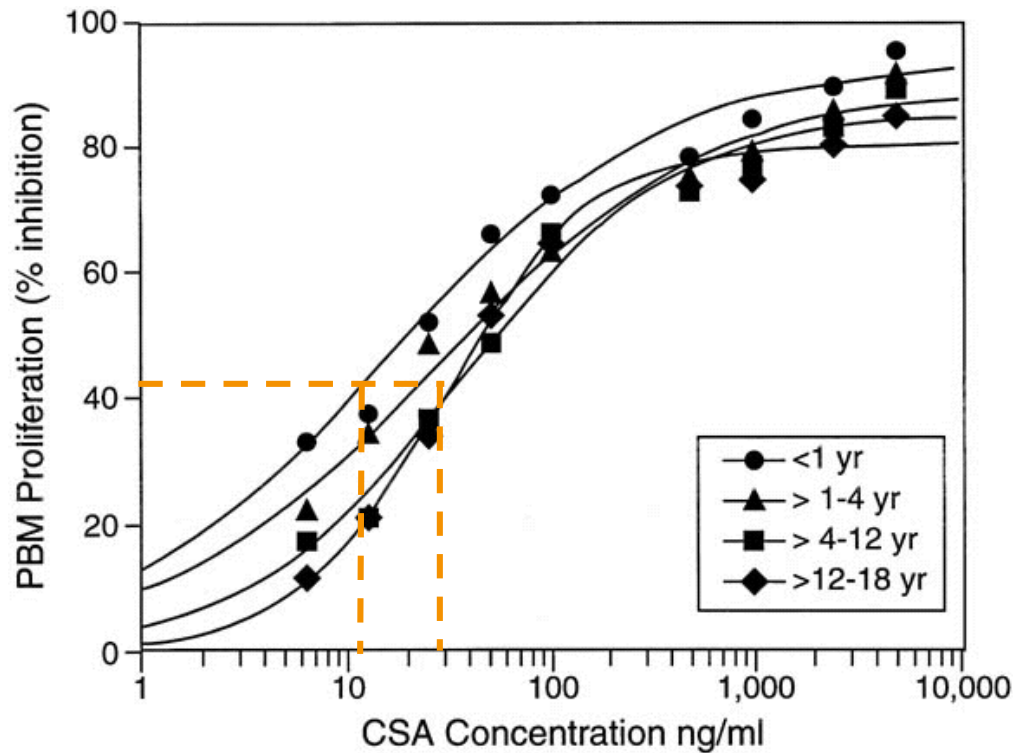
100% TERRACOTTA

100% TERRACOTTA

100% TERRACOTTA

ANNIE GRONES

# Cyclosporine Effect Is Age-Related



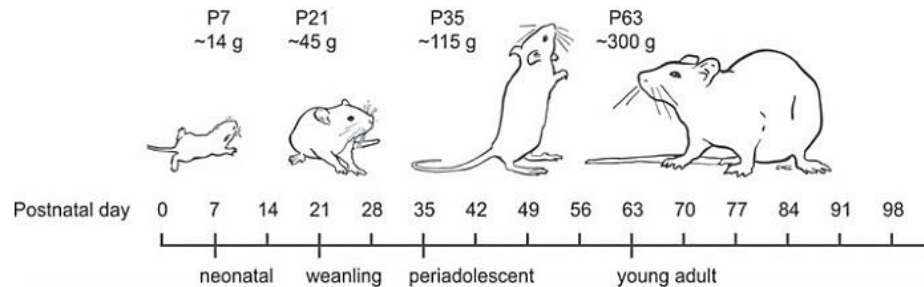
Infant lymphocyte proliferation response at EC<sub>50</sub> was 2-fold less in infants as compared to older subjects



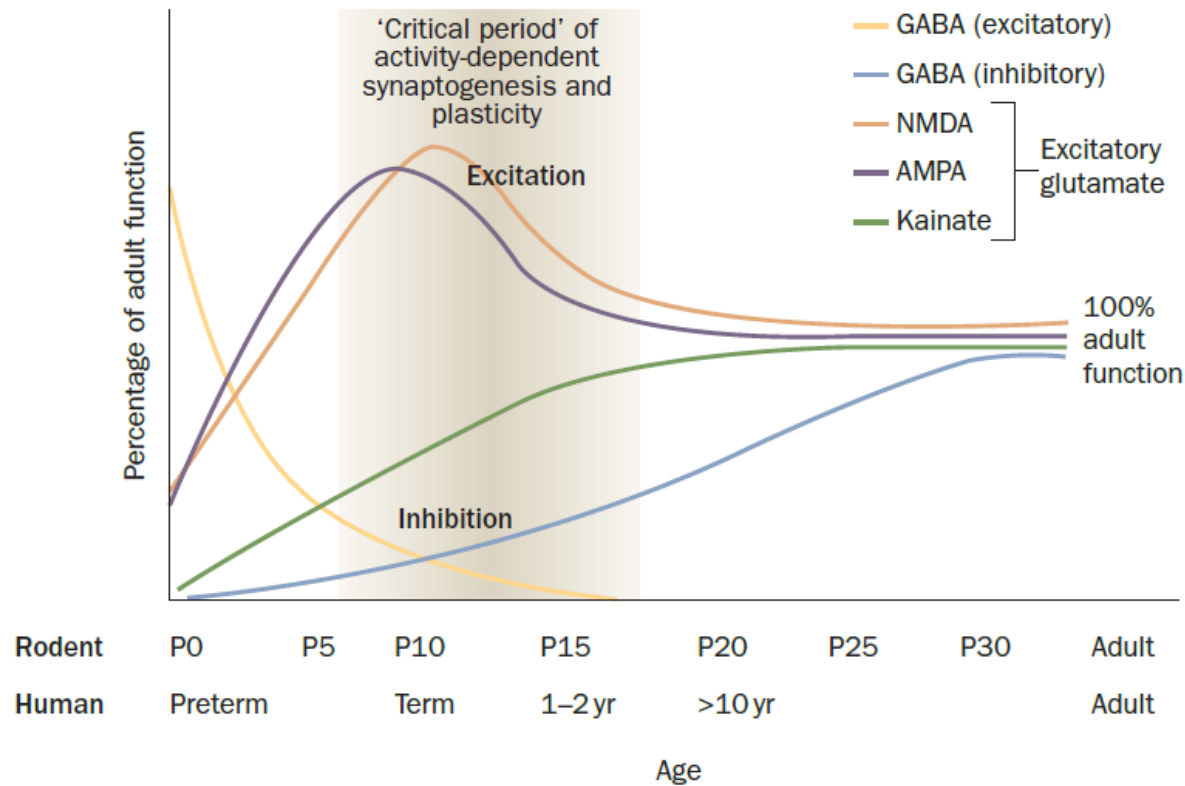
# Animal Studies in Developmental PD

- ▶ Animals are commonly used as surrogates for developmental PD studies
- ▶ Caveats
  - ▶ Different ADME
  - ▶ Different body size
  - ▶ Different receptors?
    - ▶ (e.g., neurodevelopment)

Stage	Rat	Human
Life span	3 years	80 years
Neonate	7-14 days	1 month
Weaning	21 days	6 months
Sexual maturity	50 days	11.5 years
Mature	7-8 months	20 years
Senescence	15-24 months	51 years

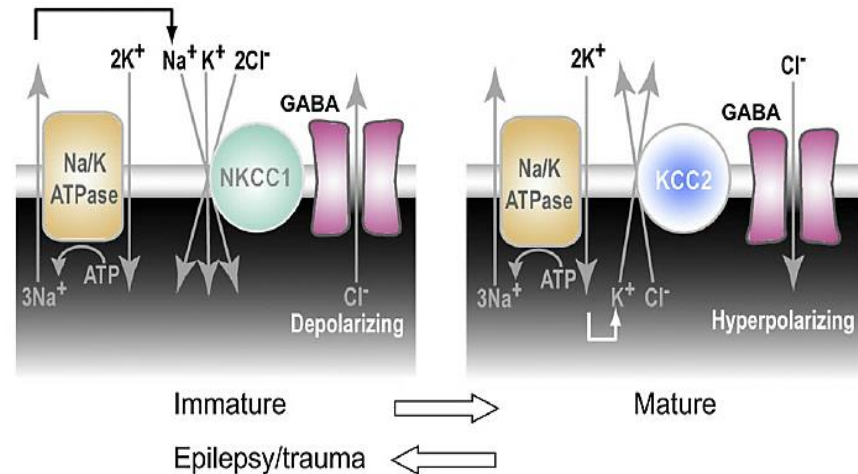


# Ontogeny of GABA & Glutamate Receptors



# Impact of Development on GABA Receptor Function

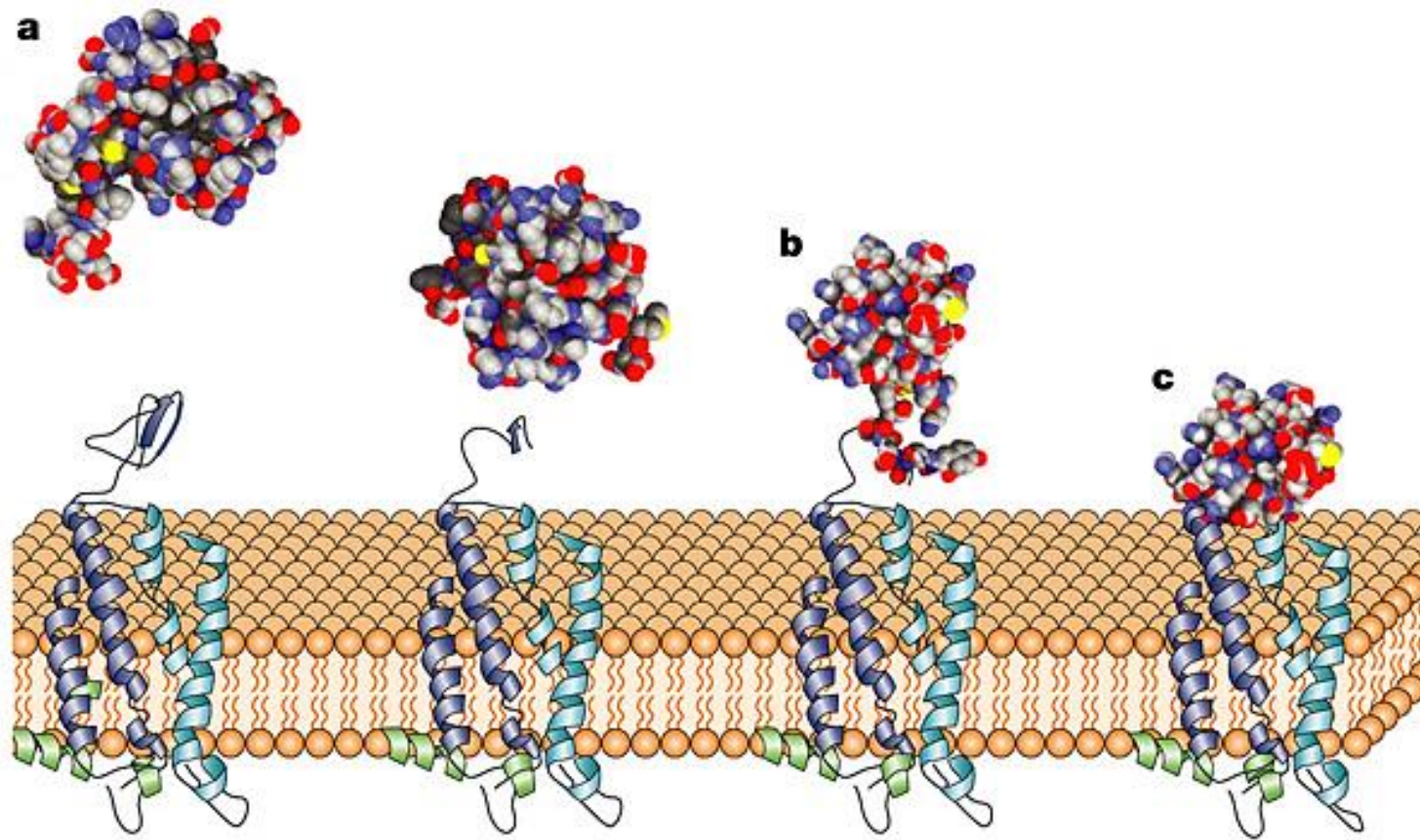
- ▶ High concentration of chloride present in nerve cells during early development, which causes excitation
- ▶ Intracellular chloride concentrations decrease during development resulting in inhibitory neurotransmitters
- ▶ GABA receptors functions differently in mature and immature subjects
  - ▶ Mature brain: inhibitory neurotransmitter
  - ▶ Immature brain: tropic factor influences proliferation, migration, differentiation, synapse maturation and cell death



# Examples of Age-Dependent Differences in Pharmacodynamics

- ▶ Higher incidence of VPA-associated hepatotoxicity in young infants
- ▶ Greater frequency of paradoxical CNS reactions to diphenhydramine in infants
- ▶ Greater weight gain associated with atypical antipsychotic agents in adolescents
- ▶ Altered warfarin dose - effect in children with congenital heart disease & prepubertal children
  - ▶ Developmental differences in Vitamin K-dependent clotting factors
  - ▶ Lower protein C concentration
  - ▶ Lower prothrombin fragments 1 and 2

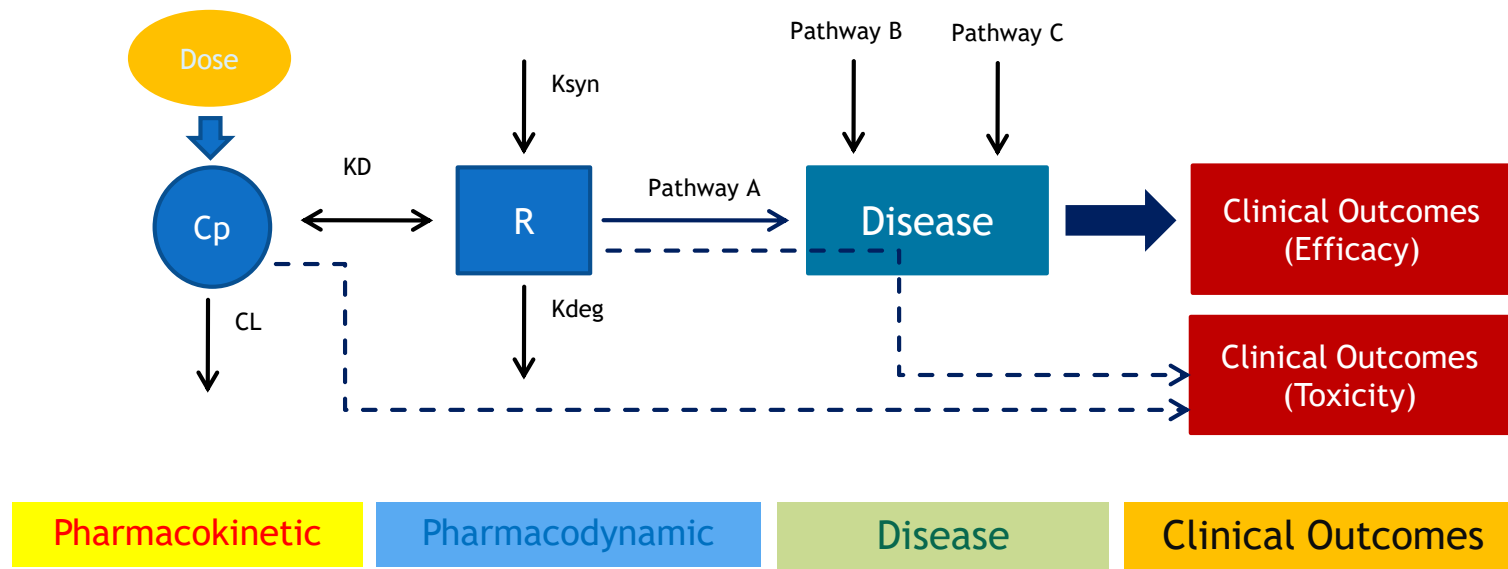




# Pharmacologic programming

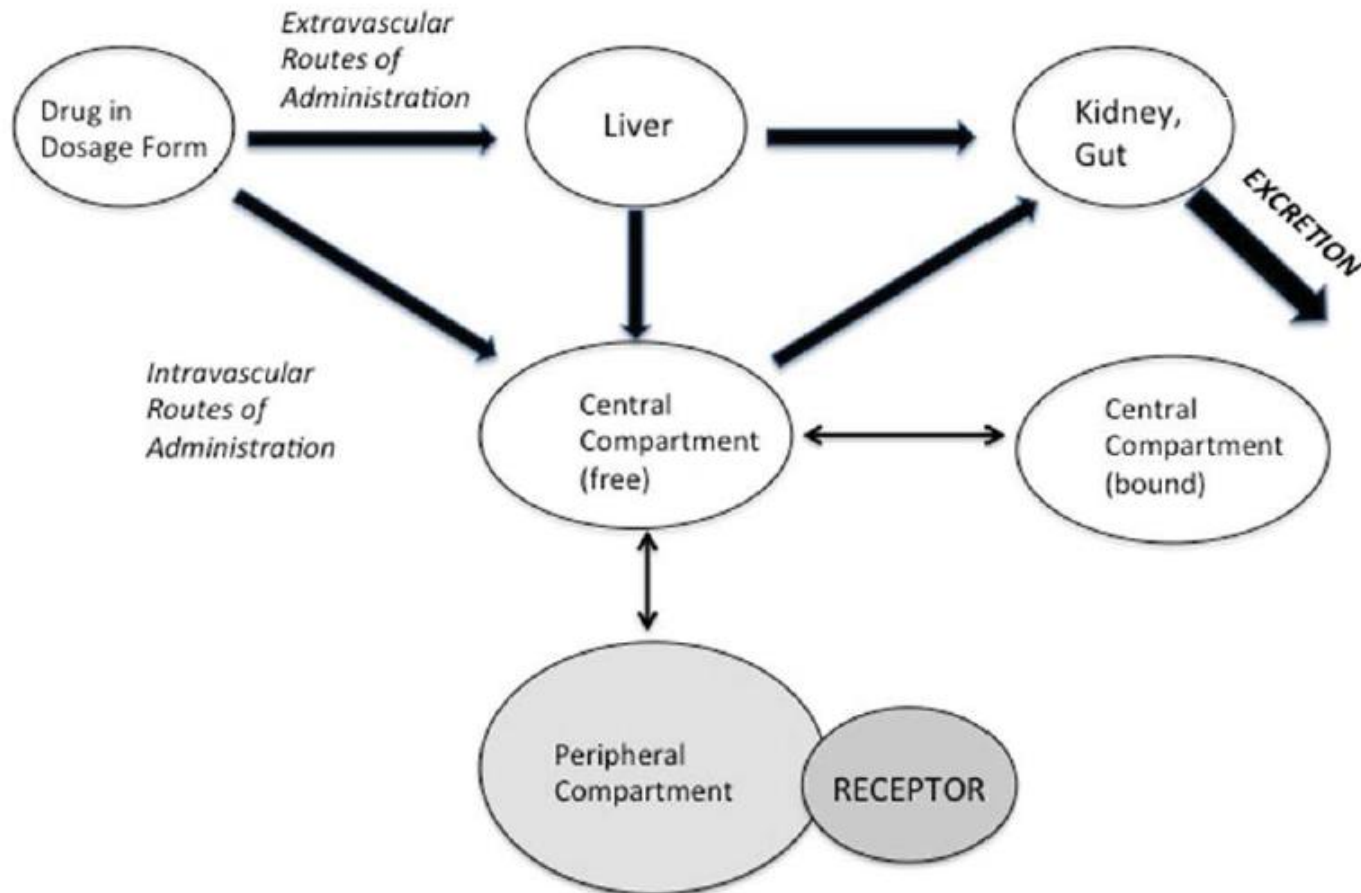
- ▶ Process whereby a drug (stimulus) applied during fetal or neonatal life has permanent effects on long-term development
- ▶ Structure and function of organ systems affected by interaction of drug with receptors during early crucial phases of development
- ▶ Can be *positive* (therapeutic) and *negative*
  - ▶ *E.g., in utero exposure to glucocorticoids adversely affects fetal renal and hepatic development as well as hypothalamus-pituitary axis development*
  - ▶ *In the developing brain, many neurotransmitters play a role entirely different from that which they play in the mature brain*

# Pharmacokinetic-Pharmacodynamic-Disease Relationships of Pharmacotherapy



# Connecting dose-exposure-response

A hypothetical compartment model linking drug administration to effect





# Assessing the Impact of Development on Drug Action and PD Will Require a New “Mouse Trap”

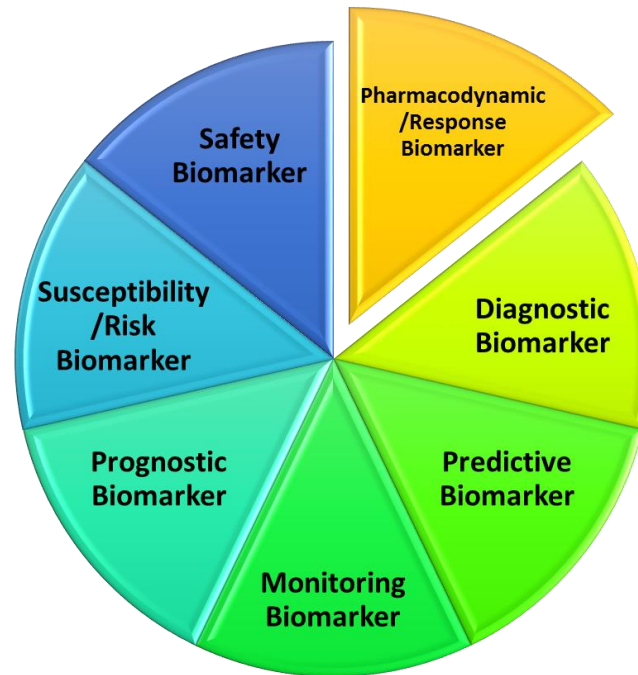


# Biomarker Definition & Categories

NIH definition: “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention.”



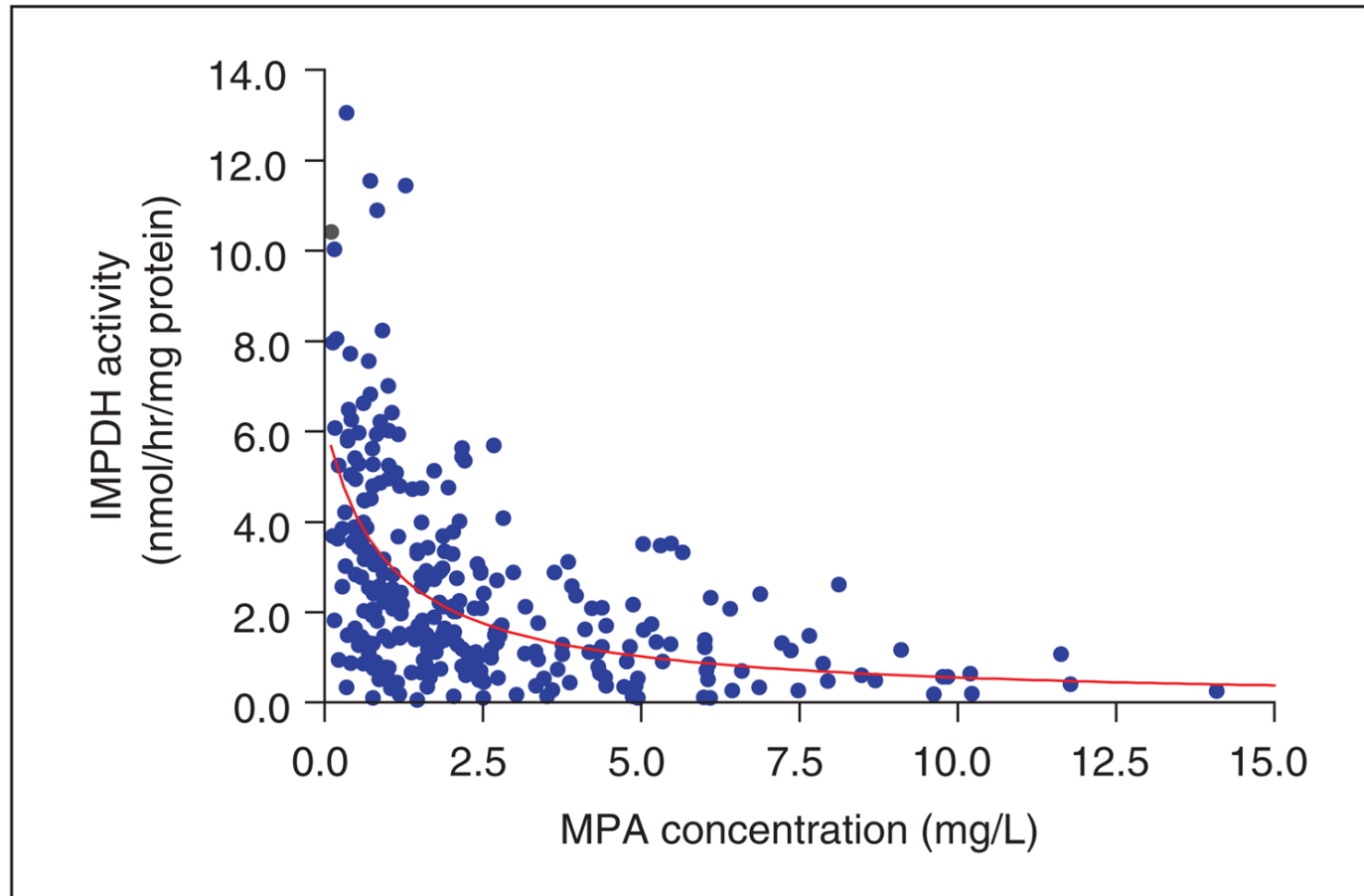
<https://www.ncbi.nlm.nih.gov/books/NBK326791/>



# Categorization of Pediatric Biomarkers

Disease Progression or Response	Systemic Drug Exposure or Effect	Pharmacodynamic Biomarkers
Hemoglobin A1C (diabetes)	CYP2D6 (codeine response)	Plasma drug concentrations
C-reactive protein (inflammation)	TPMT (azathioprine or 6-mercaptopurine effect)	PET imaging and functional MRI
Alanine aminotransferase (hepatitis C)	VKORC1 (warfarin response)	Blood pressure
Exhaled nitric oxide (asthma)	CYP2C9 (warfarin metabolism)	Epicutaneous histamine response
MYCN (neuroblastoma)	Methotrexate polyglutamates (JIA response)	Esophageal pH monitoring (gastroesophageal reflux)
C reactive protein (inflammation)	CYP2C19 (proton pump inhibitors)	AUC / MIC ratio (antimicrobial effect)

# Concentration vs. Effect - IMPDH activity as biomarker of mycophenolic acid immunosuppression





# PD/Response Biomarker

- ▶ In clinical practice: The main utility is to guide dosing or continued use of a drug or other intervention
- ▶ In drug/device development: to establish proof-of-concept that a drug produces a pharmacologic response related to clinical benefit, and to guide dose-response studies



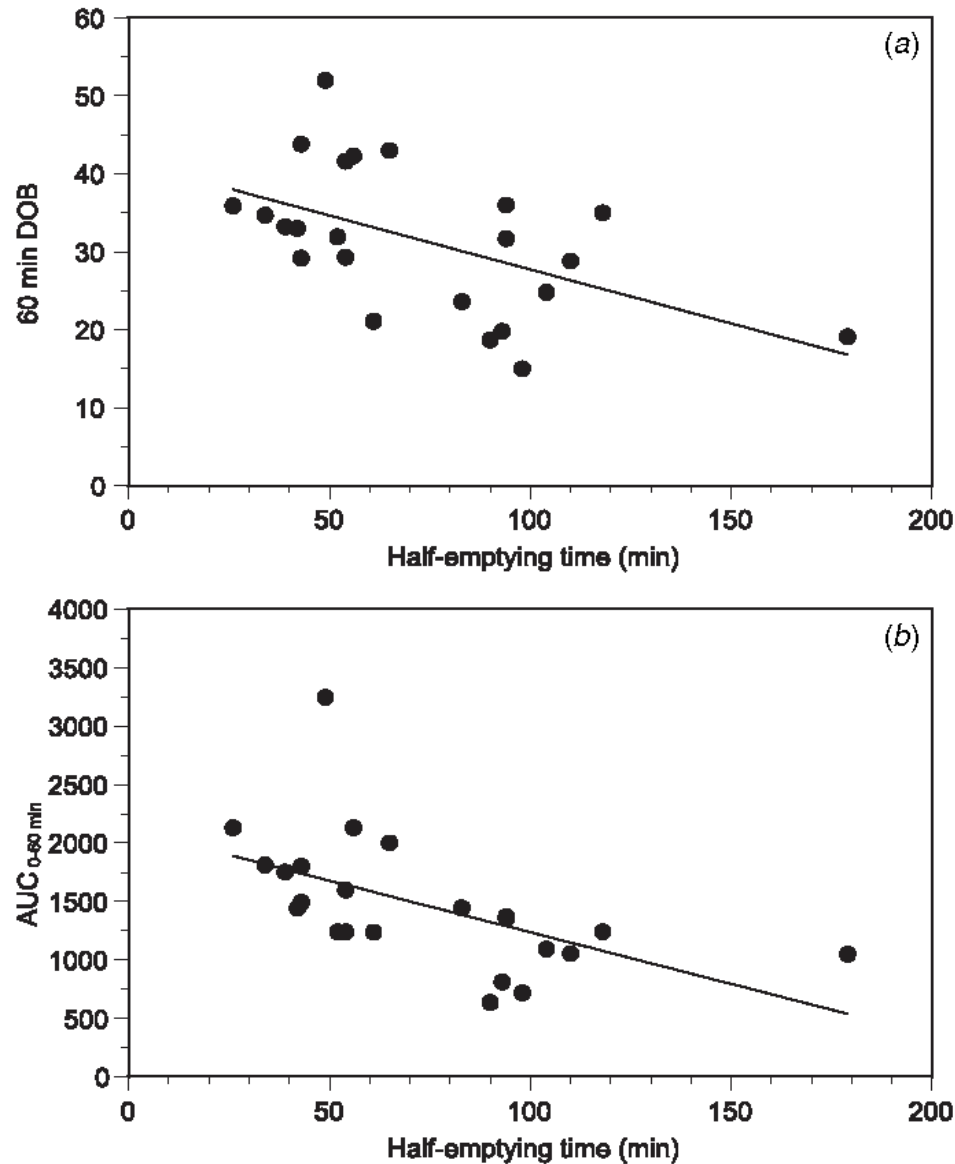
# Children are “Biomarker Orphans”

- ▶ Compared to adults, relatively few validated biomarkers are available for pediatric patients
- ▶ Specific challenges to develop biomarkers for children:
  - ▶ Lack of validated endpoints in children - often extrapolated from adult
  - ▶ Avoid invasive and repeated sampling
  - ▶ Potential impact of development on the result (e.g. ontogeny of renal function)



Of the 5 randomized, blinded trials, 2 showed no effect of metoclopramide on any outcome, and 2 showed a significant placebo effect. Four studies commented on adverse effects of therapy, with irritability being the most frequently reported potential adverse effect of therapy. Other reported adverse effects included dystonic reactions, drowsiness, oculogyric crisis, emesis, and apnea.

# $^{13}\text{C}$ Acetate Breath Test for Gastric Emptying

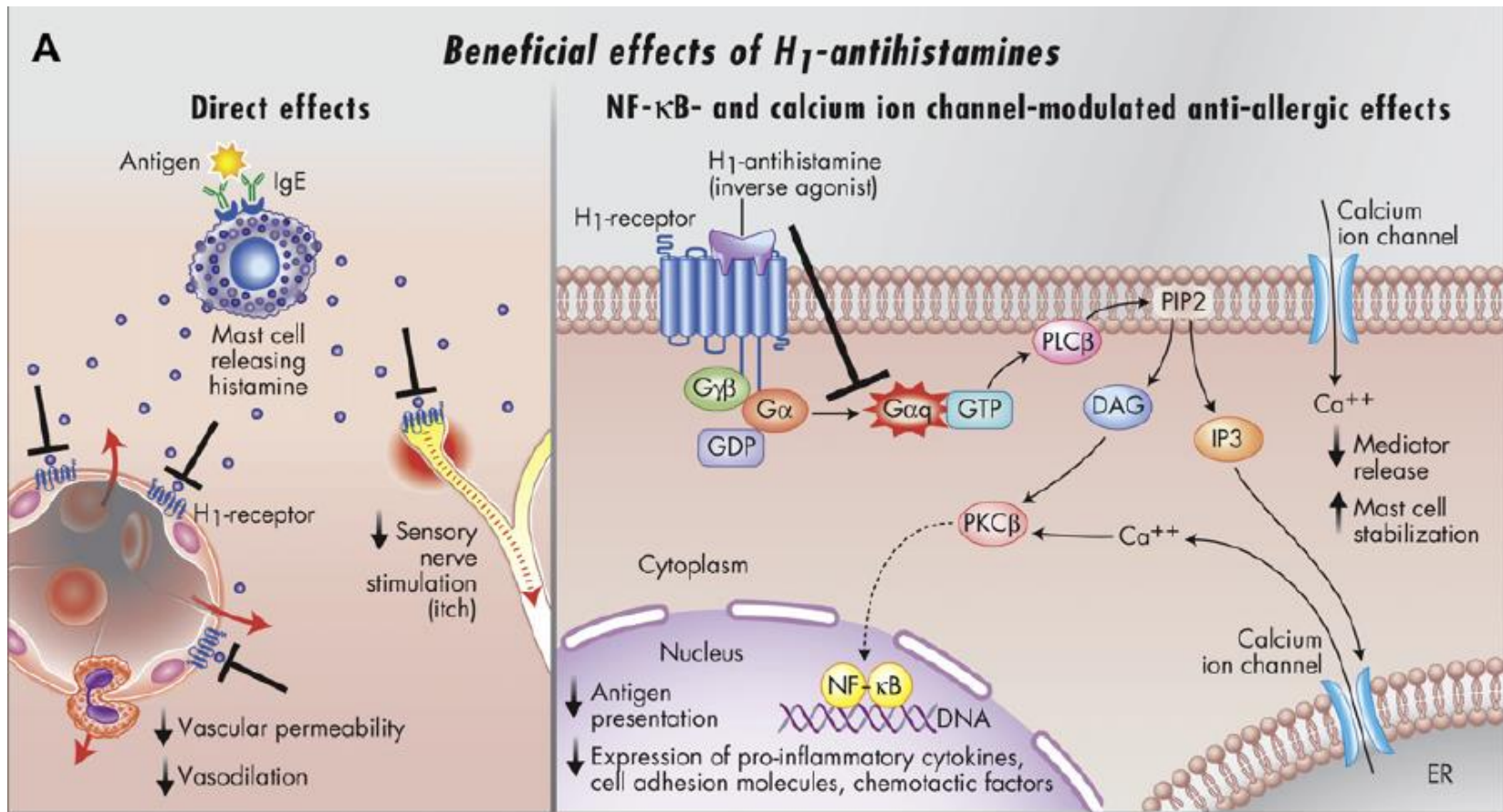




# OTC Cough and Cold Products in Children



Public Health Advisory: FDA Recommends that Over-the-Counter (OTC) Cough and Cold Products not be used for Infants and Children under 2 Years of Age

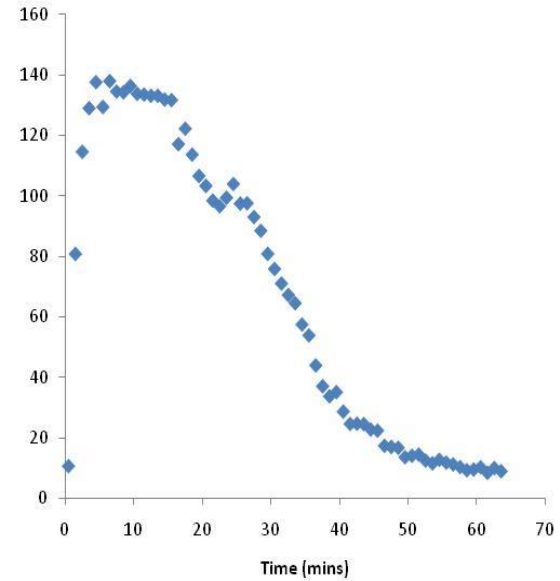
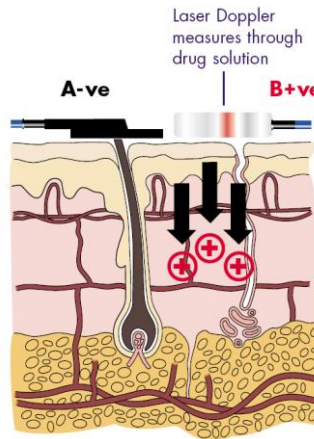
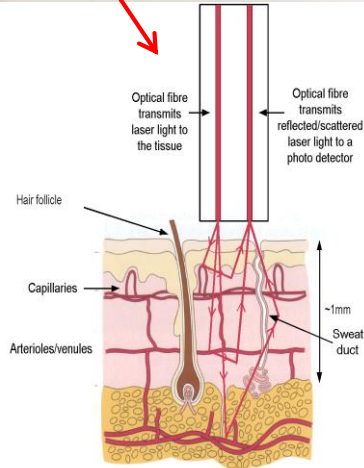


# Evaluation of Histamine Pharmacodynamics

- Epicutaneous histamine (EH) is the current “gold standard” for evaluation of histamine and antihistamine pharmacodynamics
- EH has significant limitations as a pharmacodynamic tool

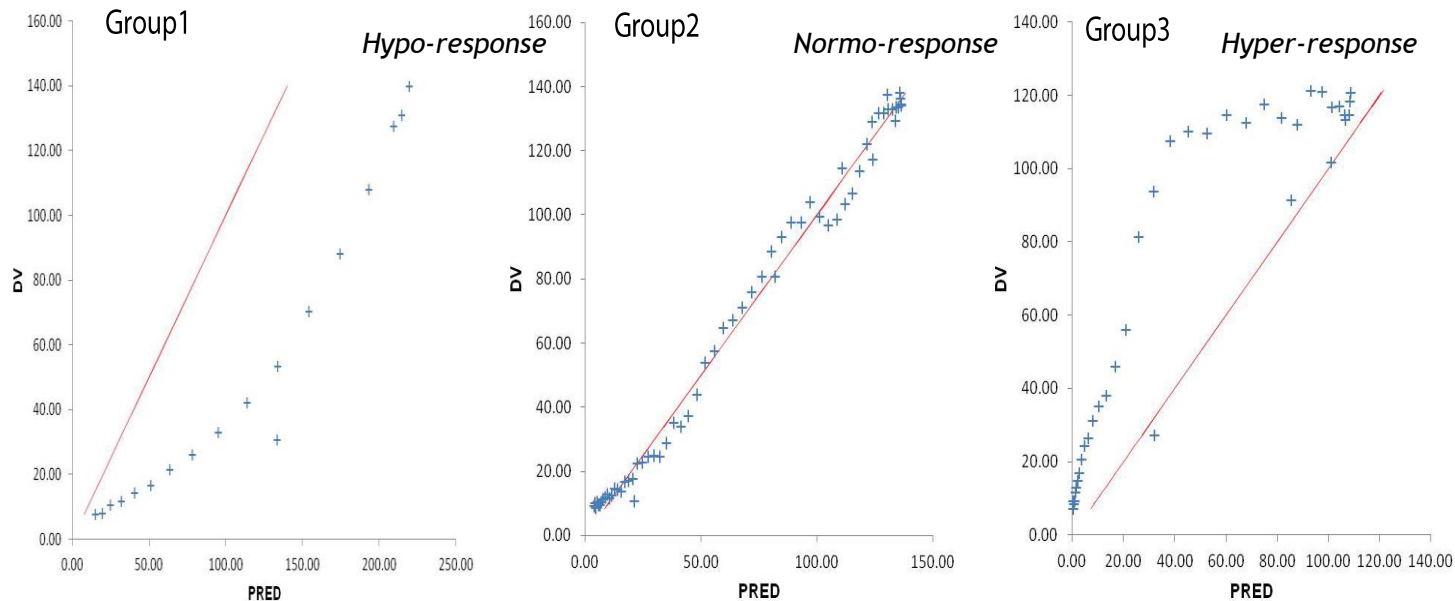


# Histamine Iontophoresis with Laser Doppler Flowimetry



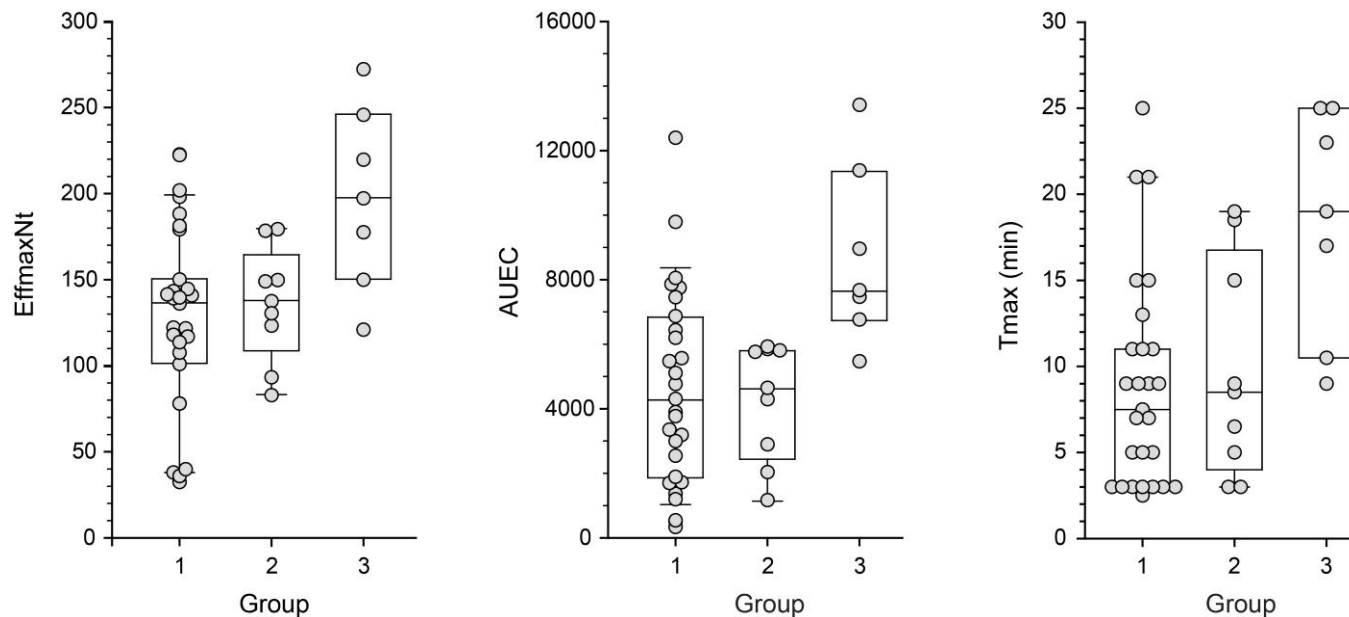
# Histamine Response Phenotypes

Distinct Groups Identified from Predicted vs. Dependent Variable Plots for each subject





# Histamine Response Phenotypes



	Group 1	Group 2	Group3*
<b>AUEC</b>	4654±2997	4233±1819	8702±2776*
<b>EffmaxNt</b>	127±52	136±33	198±53*
<b>Tmax</b>	9±6	10±6	18±7*

Mean ± standard deviation values for each response group, \*p<0.01



# Polymorphisms of Potential Importance to Determining Histamine Phenotype

## HNMT

C314T\*  
A595G  
A929G  
A1097T  
T-1637C  
T-463C  
(CA)<sub>n</sub> repeat intron 5  
BV677277(CA)<sub>n</sub>

## DAO

A-594T  
C995T  
G1329A  
C2970G  
T5052C\*  
C47T  
C4106G  
C-4586T  
C2029G\*

## H<sub>1</sub> receptor

C-17T  
G1045A  
T1522C\*  
G1047T

## H<sub>2</sub> receptor

G543A  
C826T  
G649A\*  
G-1018A

## H<sub>1</sub> receptor

C839T\*  
A280V\*

## H<sub>2</sub> receptor

ss142022671\*  
ss142022677\*  
ss142022679\*

## HDC

G951A\*

\* Denotes that variation has been found to have possible clinical significance

# Properties Required for Pediatric PD Biomarkers:

1. A predictive association with normal growth and development
2. Sufficient sensitivity to discriminate between time-dependent changes in disease pathogenesis and/or response to a treatment
3. Reasonable proximity with a drug's mechanism of action
4. Demonstration of accuracy and precision with regard to repeated measurement and sensitivity and specificity with respect to quantitation and discrimination

# Properties Required for Pediatric PD Biomarkers: (Cont'd)

5. Not be subject to epigenetic changes which could influence the phenotypic expression of disease and/or drug response.
6. Be able to be accurately and repeatedly assessed in a pediatric patient so as to enable time- and concentration-dependent study of PD
7. Be non-invasive and non-noxious (i.e., well tolerated by the patient and parents)

# Summary and Conclusions

- ▶ The use of pediatric biomarkers can add knowledge about effects of disease and ontogeny on PD
- ▶ Pediatric biomarkers require a capability of measuring drug response in both a time and age dependent fashion
- ▶ The development of pediatric biomarkers requires an integrated approach to insure that both growth and development are fully considered

# Acknowledgements

- ▶ Eunice Kennedy Shriver National Institute of Child Health and Human Development
- ▶ U.S. Food and Drug Administration
- ▶ World Health Organization
- ▶ Research collaborators at Children's Mercy Hospital and Arkansas Children's Hospital
- ▶ The Ross and Mary Whipple Family
- ▶ The staff of the Arkansas Children's Research Institute
- ▶ Research participants - patients and families

