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Appendix A

Disease Oriented Publications

Disease Oriented Publications

ADHD

Gilbert DL, Sallee FR, Zhang J, Lipps T, Wassermann EM. TMS-evoked cortical inhibition, a consistent marker of ADHD scores in Tourette Syndrome. *Biological Psychiatry*. 2005; 57: 1597-1600.

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Heart Disease

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HIV

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Appendix B

Listing of PPRU Publications in Population Pharmacokinetics

Listing of PPRU Publications in Population Pharmacokinetics

1. Meibohm B, Laer S, Panetta JC, Barrett JS. Population pharmacokinetic studies in pediatrics: issues in design and analysis. *AAPS J* 2005; 7:E475-87.
2. Vinks AA. The application of population pharmacokinetic modeling to individualized antibiotic therapy. *Int J Antimicrob Agents* 2002;19:313-22.
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6. de Wildt SN, de Hoog M, Vinks AA, Joosten KF, van Dijk M, van den Anker JN. Pharmacodynamics of midazolam in pediatric intensive care patients. *Ther Drug Monit* 2005; 27:98-102.
7. Mehta P, Vinks A, Filipovich A, et al. High-dose weekly AmBisome antifungal prophylaxis in pediatric patients undergoing hematopoietic stem cell transplantation: a pharmacokinetic study. *Biol Blood Marrow Transplant* 2006; 12:235-40.
8. Zuppa AF, Nicolson SC, Adamson PC, et al. Population pharmacokinetics of milrinone in neonates with hypoplastic left heart syndrome undergoing stage I reconstruction. *Anesth Analg* 2006;102:1062-9.
9. Aman MG, Vinks AA, Remmerie B, et al. Plasma pharmacokinetic characteristics of risperidone and their relationship to saliva concentrations in children with psychiatric or neurodevelopmental disorders. *Clin Ther* 2007; 29:1476-86.
10. Vinks AA, van Rossem RN, Mathot RA, Heijerman HG, Mouton JW. Pharmacokinetics of aztreonam in healthy subjects and patients with cystic fibrosis and evaluation of dose-exposure relationships using monte carlo simulation. *Antimicrob Agents Chemother* 2007; 51:3049-55.
11. Weimert NA, Derotte M, Alloway RR, Woodle ES, Vinks AA. Monitoring of inosine monophosphate dehydrogenase activity as a biomarker for mycophenolic acid effect: potential clinical implications. *Ther Drug Monit* 2007; 29:141-9.
12. Mondick JT, Gibiansky L, Gastonguay MR, et al. Population pharmacokinetic investigation of actinomycin-D in children and young adults. *J Clin Pharmacol* 2008; 48:35-42.

13. Tremoulet AH, Capparelli EV, Patel P, et al. Population pharmacokinetics of lamivudine in human immunodeficiency virus-exposed and -infected infants. *Antimicrob Agents Chemother* 2007; 51:4297-302.
14. Capparelli E, Hochwald C, Rasmussen M, Parham A, Bradley J, Moya F. Population pharmacokinetics of cefepime in the neonate. *Antimicrob Agents Chemother* 2005; 49:2760-6.
15. Capparelli EV, Letendre SL, Ellis RJ, Patel P, Holland D, McCutchan JA. Population pharmacokinetics of abacavir in plasma and cerebrospinal fluid. *Antimicrob Agents Chemother* 2005; 49:2504-6.
16. Capparelli EV, Englund JA, Connor JD, et al. Population pharmacokinetics and pharmacodynamics of zidovudine in HIV-infected infants and children. *J Clin Pharmacol* 2003; 43:133-40.
17. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr* 2003;142:47-52.
18. Capparelli EV, Lane JR, Romanowski GL, et al. The influences of renal function and maturation on vancomycin elimination in newborns and infants. *J Clin Pharmacol* 2001; 41:927-34.
19. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; 349:1157-67.
20. Thompson PA, Murry DJ, Rosner GL, et al. Methotrexate pharmacokinetics in infants with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol* 2007; 59:847-53.
21. Arndt C, Hawkins D, Anderson JR, Breitfeld P, Womer R, Meyer W. Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide. *J Clin Oncol* 2004; 22:1894-901.

Appendix C

Traditional PK/PD Modeling Listing of Studies

Examples of PPRU Pharmacometric Study Activity

- I. Traditional PK/PD studies - In vitro, in silico, in vitro and animal studies-used directly for PPRU study design
 - Actinomycin PK - physiologic based modeling
 - Azithromycin in mouse model for BPD - both pre-clinical PK and PD
 - Cisapride - metabolism studies performed to determine pathway for metabolite formation
 - Codeine /Morphine CSF penetration - primate modeling for pain initiative
 - Dextromethorphan – in vitro expression and characterization (kinetic) of functional consequences of newly discovered allelic variants
 - Fluticasone - reaction phenotyping used to characterize role of CYP3A4 isoforms in biotransformation
 - Lamisil – in vitro and in vivo characterization of inhibition of CYP2D6 in humans

- II. Modeling and Simulation (MS) Used in PPRU Study Design
 - Absence Epilepsy – MS used to develop dosing strategies – including compiling clinical data from to develop preliminary models. Integrated model to revise company dosing algorithm.
 - Acetaminophen protein adducts – Modeling of preliminary data used to determine sampling scheme for ADR grant application.
 - Actinomycin – PBPK modeling used with MS used to developing dosing strategies.
 - Azithromycin – MS based pediatric data to develop model for BAL concentrations and intracellular accumulation. Dosing and PK study design based on these activities.
 - Daptomycin – MS performed (PK/PD) as the basis for projection of dosing regimens for phase III pediatric program.
 - Fexofenadine – MS performed as the basis to develop design for Pop PK studies.
 - Fluconazole – MS used to determine dose. Re-analyzed data from literature. Incorporated newborn PK data and models from PK studies in simulations
 - Ibuprofen for PDA – MS used to determine dosing and sampling strategy – incorporated prior data collected outside PPRU. Used to justify study design change to FDA.
 - Inositol – ongoing MS to develop dosing for collaboration with Neonatal Network studies. Non-linear reabsorption capacity and endogenous production confounders in this model.
 - Lorazepam for Sedation – MS to determine dosing strategy with adaptive design. Initial target concentration achieved by bolus maintained by continuous infusion
 - Lorazepam for Status –MS use from initial study to develop dosing for second efficacy trial
 - Meropenem – MS used to develop dosing strategy and PK design for sampling.

- Morphine in infants – MS to determine dosing (prior dose led to toxicity). Developmental model derived from prior models including incorporation of data/models from literature.
 - Pleconaril – MS performed as the basis to develop PK aspects for pleconaril protocols in collaboration with CASG.
- III. Proteomics Discovery
- Aminoglycoside toxicity
 - APAP Toxicity
 - Azithromycin
 - Ibuprofen (Det)
 - Remicaide
- IV. Tissue based PK modeling
- Azithromycin (BPCA Proposal)
 - BAL concentrations
 - Intracellular concentrations
 - Breast Milk ARV penetration (supplemental funds)
 - Codeine Pain initiative – CSF penetration study
 - Cisapride disposition – small intestinal translocation assay
 - Meropenem (BPCA sub study)
 - Small molecule Bcl2 inhibitor tissue distribution – Infant ALL disease model (translational studies – CTSA and leukemia society funds)
- V. Clinical trials with PK/PG emphasis
- Absence Epilepsy
 - Azithromycin PK
 - Buspirone
 - Lorazepam Sedation
 - Midazolam
 - Morphine Infant Pain
 - Mycophenolic acid in renal transplant
 - Pantoprazole
- VI. Imaging research studies
- Autism
 - Early Pharmacotherapy Guided by Biomarkers in Autism
 - Utilizing PET Imaging
 - Laser Doppler flowimetry to quantitate microvascular response to drugs
 - Use of stable isotopes to quantitate gastric emptying (¹³C acetate) and DME activity (¹³C dextromethorphan)

Appendix D

Analytical Pharmacology Core Library Assays

Drug Assays Available at PPRU Sites

Assay	Drug Classification	Assay	Drug Classification
11-Deoxycortisol	Corticoids	indinavir	Antivirals
17-OH Progesterone	Sex hormones	indomethacin	NSAIDs
16OH estrone	Sex hormones	inositol	Vitamins and nutritionals
2-OH Estrone	Sex hormones	insulin	Metabolic hormones
25-OH Vit D	Vitamins and nutritionals	ISA-247	Immunomodulants
5-Fluorouracil	Antineoplastics	isoflurane	Analgesics and anesthetics
5-HIAA	Neurotransmitters	Karenitecin	Antineoplastics
5-HT	Neurotransmitters	ketamine	Analgesics and anesthetics
5-hydroxyomeprazole	Proton pump inhibitors	ketorolac	NSAIDs
5-OH bupropion	Antidepressants	LAQ824	Antineoplastics
6ketoPGFalpha	Prostaglandins	lamivudine	Antivirals
6-mercaptopurine	Immunomodulants	leptin	Metabolic hormones
6-methylmercaptopurine	Immunomodulants	levetiracetam	Anticonvulsants
6-thioguanine	Antineoplastics	levofloxacin	Quinolones
8 oxo-O6	Antineoplastics	lidocaine	Local anesthetics
abacavir	Antivirals	lidocaine metabolites	Drug metabolites
actinomycin-D	Antineoplastics	linezolid	Antibiotics
acyclovir	Antivirals	lopinavir	Antivirals
Acyl carnitines	Vitamins and nutritionals	loratadine	Antihistamines
adenylates	Metabolic substrates	mepivacaine	Local anesthetics
alfentanil	Analgesics and anesthetics	MET-enkephalin	Endorphins and enkephalins
alpha-1-acid GP	Blood proteins	metformin	Antihyperglycemics, biguanides
amantadine	Antivirals	methadone	Analgesics and anesthetics
amiloride	K+ sparing diuretics	methotrexate	Antineoplastics, immunomodulants
ampicillin	Beta-lactam antibiotics	meropenem	Beta-lactam antibiotics
amprenavir	Antivirals	Metoclopramide	Antiemetics
amoxicillin	Beta-lactam antibiotics	Metronidazole	Antifungals
ADH	Cardiorenal hormones	mexiletine	Antiarrhythmics
Androstenedione	Sex hormones	midazolam	Benzodiazepines
Angiotensin(10,8 and 7)	Cardiorenal hormones	4-OH midazolam	Drug metabolites
APA-5		1-OH midazolam	Drug metabolites
APC	Proteins	minocyclin	Tetracycline antibiotics
aprepitant	Antiemetics	MK-801	NMDA antagonists
ARV protein binding	Viral assays - HIV	morphine	Analgesics and anesthetics
aspirin	NSAIDs, salicylates	morphine metabolites	Drug metabolites
atazanavir	Antivirals	moxifloxacin	Quinolones

Assay	Drug Classification	Assay	Drug Classification
beclamethasone	Corticoids	mycophenolic acid	Immunomodulators
benzylguanine	Antineoplastics	nafcillin by bioassay	Beta-lactam antibiotics
beta-endorphin	Endorphins and enkephalins	naloxone	Antidotes
bile acids (total)	Digestive substances	nelfinavir	Antivirals
Bumetanide	Loop diuretics	nelfinavir-M8	Drug metabolites
bupivacaine	Local anesthetics	NNRTIs (EFV, DLV, NVP)	Antivirals
buprenorphine	Analgesics and anesthetics	NNRTIs/PIs (NVP, IDV, DRV, APV, NFV, SQV, ATV, EFV, RTV, LPV, and TPV)	Antivirals
Bupropion	Antidepressants	NRTIs (ddC, 3TC, ddl, d4T, AZT, ABC, NVP)	Antivirals
C.P.M. - gamma	Radiation	NRTIs/PIs/NNRTIs (ZDV, ddl, ddC, d4T, 3TC, ABC, EFV, DEL, NVP, TFV, IDV, APV, NFV, SQV, ATV, RTV, and LPV)	Antivirals
caffeine	CNS stimulants, purines	NGF	Growth hormones
Carboplatin	Antineoplastics	NPY	Neurotransmitters
carnitine	Vitamins and nutritionals	O6 benzylguanine	Antineoplastics
catecholamines	Neurotransmitters	omeprazole	Proton pump inhibitors
cefepime	Beta-lactam antibiotics	omeprazole sulfide (CYP2C19)	Drug metabolites
Cefpodoxime	Beta-lactam antibiotics	omeprazole sulphone	Drug metabolites
Ceftazadime	Beta-lactam antibiotics	ondansetron	Antiemetics
cetirizine	Antihistamines	Oxytocin	Neurotransmitters
CGRP	Vasoactive substances	paraxanthine	CNS stimulants, xanthines
ciprofloxacin	Quinolones	paroxetine	SSRIs
citalopram	SSRIs	pentoxiflline	Blood modifiers
CI-994	Antineoplastics	PGE2	Prostaglandins
clindamycin	Lincomycin-like antibiotics	Phenylacetate	Antineoplastics
clonidine	Alpha-2 agonists	Phenylacetylglutamine	Drug metabolites
codeine	Analgesics and anesthetics	Phenylbutyrate	Miscellaneous drugs
Corticosterone	Corticoids	piperacillin	Beta-lactam antibiotics
cortisol	Corticoids	Plasticizers	Extraneous inactive compounds
cotinine	Drug metabolites	Pralidoxime	Antidotes
CPT-11	Antineoplastics	prednisone	Corticoids
Cyclosporine	Immunomodulators	Procabazine	Antineoplastics
D.P.M. - 14C	Radiation	Progesterone	Corticoids
D.P.M. - 3H	Radiation	propofol	Sedatives - other
D.P.M. - 3H&14C	Radiation	protein (total)	Blood proteins
daptomycin	Peptide antibiotics	Pyrabenzamide	Antihistamines (pyrabenzamine?)
dasatinib	Antineoplastics	PYY	Metabolic hormones

Assay	Drug Classification	Assay	Drug Classification
Daunomycin, daunomycinol	Antitumor antibiotics	quinupristin/dalfopristin	Streptogramin antibiotics
Depsipeptide	Antineoplastic peptides	ranitidine	H2 antagonists
desipramine	Antidepressants	RBC Fatty Acids	Blood components
dexmedetomidine	Sedatives - other	Rebeccamycin	Antitumor antibiotics
dextromethorphan	Antitussives, hallucinogens	rifampin	Antituberculosis drugs
dextrorphan (CYP2D6)	Drug metabolites	riluzole	CNS drugs, miscellaneous
DHEA/DHEAS	Sex hormones	risperidone	Antipsychotics - novel
diazepam	Benzodiazepines	ritonavir	Antivirals
didanosine	Antivirals	S-100	Tumor markers
Digoxin (P-glycoprotein)	Digitalis cardiac glycosides	saquinavir	Antivirals
Diindolylmethane	Antineoplastics	sertraline	SSRIs
diphenhydramine	Antihistamines	Sirolimus	Immunomodulants
DNA-J	Genetic testing	SN-38	Antineoplastics
Doxorubicin, doxorubicinol	Antitumor antibiotics	SN-38 glucuronide	Drug metabolites
ECP	Miscellaneous?	ST-91	Cardiovascular drugs
efavirenz	Antivirals	STI-571	Antineoplastics
emtricitabine	Antivirals	SU-5416	Antineoplastics
EPx	Genetic testing	substance P	Neurotransmitters
esmolol	Beta blockers	sufentanil	Analgesics and anesthetics
estradiol	Sex hormones	sulbactam	Beta-lactamase inhibitor
estriol	Sex hormones	T4/T3/FT4/FT3	Metabolic hormones
estrone	Sex hormones	tacrolimus	Immunomodulants
Etoposide	Antineoplastics	Taxol	Antineoplastics
Everolimus	Immunomodulants	Taxotere	Antineoplastics
excitatory amino acids	Neurotransmitters	TDF/FTC	Antivirals
extraction - CSF	Extraction	temozolamide	Antineoplastics
extraction - plasma	Extraction	Tenofovir	Antivirals
extraction - tissue	Extraction	testosterone	Sex hormones
famotidine	H2 antagonists	Thalidomide	Antineoplastics, antileptotics
fentanyl	Analgesics and anesthetics	THC - Test Article	Assay - 'recreational' drug use
fluconazole	Antifungals	THC metabolites - MS	Assay - 'recreational' drug use
flunisolide	Corticoids	THC plasma - ELISA	Assay - 'recreational' drug use
fluoxetine	Antidepressants	tipranavir	Antivirals
fluticasone	Corticoids	TNFalpha	Cytokines
Forskolin	Miscellaneous, terpenes	tobramycin (by florescence polarization)	Aminoglycoside antibiotics
GABA	Neurotransmitters	Topotecan	Antineoplastics
gabapentin	Anticonvulsants	trazadone	Antidepressants
Ganciclovir	Antivirals	triamcinolone	Corticoids

Assay	Drug Classification	Assay	Drug Classification
Gangliosides (GM1 and GM2)	Tumor markers	tryptophan	Amino acids
gatifloxacin	Quinolones	uracil	Pyrimidines
Gemcitabine	Antineoplastics	uridine	Nucleosides
gentamicin	Aminoglycoside antibiotics	urine 10 panel screen	Assay - 'recreational' drug use
ghrelin	Digestive hormones	vancomycin	Glycopeptide antibiotics
glyburide	Antihyperglycemics, sulfonylureas	venlafaxine	SSRIs
HGF	Growth hormones	vinblastine	Antineoplastics
histamine	Neurotransmitters	vincristine	Antineoplastics
hydrocodone	Analgesics and anesthetics	Warfarin	Blood modifiers
ibuprofen	NSAIDs, propanoic acids	zalcitabine	Antivirals
IL1	Cytokines	zidovudine	Antivirals
IL12	Cytokines	most drugs of abuse	Assay - 'recreational' drug use
IL6	Cytokines		
IL8	Cytokines		

Appendix E

PG Publications Emanating from the PPRU Network

PPRU Network Publications Involving Pharmacogenetics / Pharmacogenomics 1998 to 2008

Studies Exploring Developmental Pharmacogenomics (Ontogeny)

1. **Blake MJ, Abdel-Rahman SM, Pearce RE, Leeder JS, Kearns GL.** Effect of diet on the development of drug metabolism by cytochrome P-450 enzymes in healthy infants.
2. *Pediatr Res* 2006; 60(6): 717-23.
3. **Blake MJ, Gaedigk A, Pearce RE, Bomgaars LR, Christensen ML, Stowe C, James LP, Wilson JT, Kearns GL, Leeder JS.** Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. *Clin Pharmacol Ther* 2007; 81(4): 510-6.
4. Allegaert K, van Schaik RH, Vermeersch S, Verbesselt R, Cossey V, Vanhole C, van Fessem M, de Hoon J, **van den Anker JN.** Postmenstrual age and CYP2D6 polymorphisms determine tramadol O-demethylation in critically ill neonates and infants. *Pediatr Res* 2008 (in press)
5. **Leeder JS, Gaedigk R, Marcucci KA, Gaedigk A, Vyhldal CA, Schindel BP, Pearce RE.** Variability of CYP3A7 expression in human fetal liver. *J Pharmacol Exp Ther.* 2005; 314: 626-635.
6. **Vyhldal CA, Gaedigk R, Leeder JS.** Nuclear receptor expression in fetal and pediatric liver: correlation with CYP3A expression. *Drug Metab Dispos.* 2006; 34: 131-137.
7. **Gaedigk A, Baker DW, Totah RA, Gaedigk R, Pearce RE, Vyhldal CA, Zeldin DC, Leeder JS.** Variability of CYP2J2 expression in human fetal tissues. *J Pharmacol Exp Ther.* 2006; 319: 523-532.
8. **Kearns GL, Robinson PK, Wilson JT, Wilson-Costello D, Knight GR, Ward RM, van den Anker JN;** Pediatric Pharmacology Research Unit Network. Cisapride disposition in neonates and infants: in vivo reflection of cytochrome P450 3A4 ontogeny. *Clin Pharmacol Ther.* 2003; 74: 312-325.
9. Matei KE, **Vyhldal CA, Le M, Klick D, Hines RN.** Regulation of CYP3A4 Expression by PAR Transcription Factors. *FASEB J* 2007; 21: A1183

Pharmacogenetic/Pharmacogenomic Studies Supporting Clinical Trials

1. Saitoh A, Sarles E, **Capparelli E, Aweeka F, Kovacs A, Burchett SK, Wiznia A, Nachman S, Fenton T, Spector SA.** CYP2B6 genetic variants are associated with nevirapine pharmacokinetics and clinical response in HIV-1 Infected Children. *AIDS* 2007 21:2191-2199.

2. Shelepova T, Nafziger AN, Victory J, Kashuba ADM, Rowland E, Zhang Y, Sellers E, **Kearns G, Leeder JS, Gaedigk A**, Bertino JS. Effect of a triphasic oral contraceptive on drug metabolizing enzyme activity as measured by the validated Cooperstown 5+1 cocktail. *Journal of Clinical Pharmacology*. 2005;45(12):1413-21.
3. Ma JD, Nafziger AN, Villano SA, **Gaedigk A**, Bertino JS. Maribavir pharmacokinetics and the effects of multiple-dose maribavir on cytochrome P450 (CYP) 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A, N-acetyltransferase-2, and xanthine oxidase activities in healthy adults. *Antimicrobial Agents and Chemotherapy*. 2006;50(4):1130-5.
4. Heresi GP, Gerstmann DR, **Reed MD, van den Anker JN, Blumer JL**, Kovanda L, Keirns JJ, Buell DN, **Kearns GL**. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. *Pediatric Infectious Disease Journal*, 2006; 25(12):1110-5 [sub-study of COMT genotyping]
5. **Edwards DJ**, Fitzsimmons ME, Schuetz EG, Yasuda K, Ducharme MP, Warbasse LH, Woster PM, Schuetz JD, Watkins P. 6',7'-Dihydroxybergamottin in grapefruit juice and Seville orange juice: effects on cyclosporine disposition, enterocyte CYP3A4, and P-glycoprotein. *Clinical Pharmacology & Therapeutics*. 1999; 65(3): 237-244.
6. Nowak SN, **Edwards DJ**, Clarke A, Anderson GD, Jaber LA. Pioglitazone: effect on CYP3A4 activity. *Journal of Clinical Pharmacology*. 2002; 42: 1299-1302.
7. DiMarco MP, **Edwards DJ**, Wainer IW, Ducharme MP. The effect of grapefruit juice and Seville orange juice on the pharmacokinetics of dextromethorphan: The role of gut CYP3A and P-glycoprotein. *Life Science*. 2002; 71: 1149-1160.
8. Kim JS, Nafziger AN, **Gaedigk A**, Dickmann L, Rettie A, **Kearns GL**, Bertino JS. Effects of oral vitamin k on s- and r- warfarin pharmacokinetics and pharmacodynamics: enhanced safety of warfarin as a CYP2C9 probe. *Clinical Pharmacology & Therapeutics*. 2001; 41(7):715-22.
9. **Kearns GL**, Andersson T, **James LP**, Li BUK, **Gaedigk A**, Kraynak RA, Ramabadran K, **Abdel-Rahman SM, van den Anker JN**, the PPRU Network. Omeprazole disposition in children following single-dose administration: relationship to CYP2C19 genotype. *Journal of Clinical Pharmacology*. 2003; 43: 840-848.
10. Droll K, Bruce-Mensah K, Otton SV, **Gaedigk A**, Sellers EM, Tyndale RF. Comparison of three CYP2D6 probe substrates and genotype in Ghanaians, Chinese, and Caucasians. *Pharmacogenetics*, 1998; 8: 325-333.

11. Kashuba ADM, Nafziger AN, **Kearns GL, Leeder JS**, Shirey CS, **Gotschall RR, Gaedigk A**, Bertino JS. Quantification of three-month intraindividual variability and the influence of menstrual cycle phase on CYP2D6 activity as measured by dextromethorphan phenotyping. *Pharmacogenetics*, 1998; 8: 403-410.
12. Kashuba AD, Nafziger AN, **Kearns GL, Leeder JS, Gotschall R**, Rocci ML Jr, Kulawy RW, Beck DJ, Bertino JS Jr. Effect of fluvoxamine therapy on the activities of CYP1A2, CYP2D6, and CYP3A as determined by phenotyping. *Clin Pharmacol Ther.* 1998; 64: 257-268.
13. Trepanier EF, Nafziger AN, **Kearns GL**, Kashuba AD, Amsden GW. Absence of effect of terbinafine on the activity of CYP1A2, NAT-2, and xanthine oxidase. *J Clin Pharmacol.* 1998; 38: 424-428.
14. Streetman DS, Bleakley JF, Kim JS, Nafziger AN, **Leeder JS, Gaedigk A, Gotschall R, Kearns GL**, Bertino JS Jr. Combined phenotypic assessment of CYP1A2, CYP2C19, CYP2D6, CYP3A, NAT2, and XO with the "Cooperstown Cocktail". *Clin Pharmacol Ther.* 2000: 375-383.
15. **Abdel-Rahman SM, Leeder JS**, Wilson JT, **Gaedigk A, Gotschall RR**, Medve R, Liao S, Spielberg SP, **Kearns GL**. Concordance between tramadol and dextromethorphan parent/metabolite ratios: the influence of CYP2D6 and non-CYP2D6 pathways on biotransformation. *J Clin Pharmacol.* 2002; 42: 24-29.
16. Chainuvati S, Nafziger AN, **Leeder JS, Gaedigk A, Kearns GL**, Sellers E, Zhang Y, Kashuba Ad, Rowland E, Bertino JS Jr. Combined phenotypic assessment of cytochrome p450 1A2, 2C9, 2C19, 2D6, and 3A, N-acetyltransferase-2, and xanthine oxidase activities with the "Cooperstown 5+1 cocktail". *Clin Pharmacol Ther.* 2003; 74: 437-447.
17. Ma JD, Nafziger AN, Kashuba AD, Kim MJ, **Gaedigk A**, Rowland E, Kim JS, Bertino JS Jr. Limited sampling strategy of S-warfarin concentrations, but not warfarin S/R ratios, accurately predicts S-warfarin AUC during baseline and inhibition in CYP2C9 extensive metabolizers. *J Clin Pharmacol.* 2004; 44: 570-576.
18. Zineh I, Beitelshes AL, **Gaedigk A**, Walker JR, Pauly DF, Eberst K, **Leeder JS**, Phillips MS, Gelfand CA, Johnson JA. Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin. Pharmacol. Ther.* 2004; 76: 536-544.
19. Kim MJ, Nafziger AN, Kashuba AD, Kirchheiner J, Bauer S, **Gaedigk A**, Bertino JS Jr. Effects of fluvastatin and cigarette smoking on CYP2C9 activity measured using the probe S-warfarin. *Eur J Clin Pharmacol.* 2006; 62: 431-436.

20. Findling RL, Nucci G, Piergies AA, Gomeni R, Bartolic EI, Fong R, Carpenter DJ, **Leeder JS, Gaedigk A, Danoff TM**. Multiple-dose pharmacokinetics of paroxetine in children and adolescents with major depressive disorder or obsessive-compulsive disorder. *Neuropsychopharmacology* 2006;31:1274-1285

Pharmacogenomics of Disease Expression

1. **Kennedy MJ**, Scripture CD, Kashuba ADM, Scott CS, **Gotschall RR, Gaedigk A, Kearns GL**. Assessment of hepatic enzyme activity in children with cystic fibrosis using caffeine and dextromethorphan phenotyping. *Clinical Pharmacology & Therapeutics*. 2004; 75(3): 163-171.
2. Englund JA, Raskino C, Vavro C, Palumbo P, Ross LL, **McKinney RE**, Nikolic-Djokic D, Colgrove RC, Baker CJ. Mutations linked to drug resistance, human immunodeficiency type 1 biologic phenotype and their association with disease progression in children receiving nucleoside reverse transcriptase inhibitors. *Pediatric Infectious Disease Journal*. 2004; 23: 15-22.
3. Li D, Jiao L, Li Y, Doll MA, Hein DW, Bondy ML, Evans DB, Wolff RA, Lenzi R, Pisters PW, Abbruzzese JL, Hassan MM. Polymorphisms of cytochrome P4501A2 and N-acetyltransferase genes, smoking and risk of pancreatic cancer. *Carcinogenesis* 2006;27(1):103-11.
4. Darbari DS, Minniti C, Rana S, **van den Anker JN**. Pharmacogenetics of morphine: Potential implications in sickle cell disease. *Am J Hematol* 2007 Aug 23; [Epub ahead of print]
5. Darbari DS, van Schaik RH, Capparelli EV, Rana S, van der Werf, McCarter R, **van den Anker JN**. UGT2B7 promotor variant -840G>A contributes to variability in hepatic clearance of morphine in patients with sickle cell disease. *Am J Hematol* 2007 Aug 27; [Epub ahead of print]
6. **Gaedigk A, Gaedigk R, Abdel-Rahman SM**. Genetic Heterogeneity in the rRNA Gene Locus of *Trichophyton tonsurans*. *J Clin Microbiol*. 2003; 41: 5478-5487.
7. **Abdel-Rahman SM, Preuett B, Gaedigk A**. Multilocus genotyping identifies infections by multiple strains of *Trichophyton tonsurans*. *J Clin Microbiol*. 2007; 45: 1949-1953.
8. **Leeder JS, Lu X, Timsit Y, Gaedigk A**. Non-monoxygenase cytochromes P450 as potential human autoantigens in anticonvulsant hypersensitivity reactions. *Pharmacogenetics*, 1998; 8: 211-225.

9. Kim MJ, Bertino JS, Jr., **Gaedigk A**, Zhang Y, Sellers EM, Nafziger AN. Effect of sex and menstrual cycle phase on cytochrome P450 2C19 activity with omeprazole used as a biomarker. *Clin Pharmacol Ther.* 2002; 72: 192-199.
10. **Abdel-Rahman SM**, Simon S, **Wright KJ**, Ndjountche L, **Gaedigk A**. Tracking *Trichophyton tonsurans* through a large urban child care center: defining infection prevalence and transmission patterns by molecular strain typing. *Pediatrics.* 2006; 118: 2365-2373.
11. Bhatena A, **Gaedigk R**, **Abdel-Rahman SM**. Characterization of the ALP1 gene locus of *Trichophyton tonsurans*. *Mycopathologia.* 2005; 160: 265-272.

Studies Exploring Gene Frequency and/or Genotype / Phenotype Association

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Appendix F

PPRU Data Repository White Paper

PPRU Clinical Data Repository (PeDaR)

SUMMARY

The development of a process and environment to capture, store and visualize PPRU-generated data is being pursued by a sub-team of the PPRU Network with the intention of developing a strategy and proposal for broader dissemination, feedback and eventual acceptance. In conjunction with the NIH Roadmap Initiative as well as NIH's data sharing policy, this effort aims to provide a standardized, secure environment to house data generated within the PPRU. While the primary focus of the effort will be constructed around ongoing and future trials, there will be a strategy to accumulate historical data as well. The proposed PPRU Clinical Data Repository (PeDaR) will provide a single secure location for the storage of all investigator initiated study data to promote data sharing and meta data analysis. The foundation of the PeDaR is built upon existing and widely adopted standards such as CDISC and BRIDG models. In addition, the PPRU Repository PK module potential to provide additional analysis capabilities is also discussed along with the potential for linking to additional data stores (e.g., non-PPRU data). The purpose of this document is to garner feedback from the PPRU investigators so that a more definitive path forward can be defined and that an agreement with the various stakeholders can be pursued.

BACKGROUND

In 1994, NICHD formed the Pediatric Pharmacology Research Units (PPRU) Network to address the information gaps regarding the safety and efficacy of pediatric drugs and the Pediatric Plan published by FDA's Center for Drug Evaluation and Research (CDER). The PPRU mission is to develop and disseminate new information that facilitates drug development and improves drug therapy for children. The Network has evolved over the 13 years since its inception and currently its focus reflects the increasing biological complexity in research.

Early drug oriented therapeutics focused on pharmacokinetic (PK) and labeling studies and understanding drug response and drug disposition. The focus evolved to exploring disease oriented therapeutics and increasingly is directed to understanding patient oriented therapeutics and the molecular determinants of drug responsiveness to explain pharmacokinetics, pharmacogenetics (PG), drug toxicity, genomics, proteomics, modeling, and lack of efficacy. To address these research areas, the PPRU performs PK studies (Phase I-II), PK/PD investigations and translation science integrating drug metabolism and PG and proteomics. Innovative approaches to trial design and execution enable the Network to explore the effects of childhood development on the pharmacokinetics of drugs, the influence of age-specific changes in drug disposition and pharmacodynamics, and the interplay between disease states and stage of development. The PPRU Network sites are conducting clinical studies in a wide array of therapeutic areas. Interventions for common disorders, such as allergies, asthma, and upper respiratory infections, as well as less common disorders, such as cystic fibrosis, severe infections, AIDS, sickle cell anemia, cancer, and childhood depression have been studied

by the Network.

The PPRU has been extremely productive during its existence and its output can be measured in patient experience. From 1994 through June of 2007, 9292 children have been enrolled in 264 studies (161 designed/co-designed by industry sponsor and 103 designed by investigator). While much of these data have been used in various publications, submitted to NIH and/or FDA and presented in various scientific forums, the location of the actual source data may be unknown. While there have been efforts to pool data for various meta analyses, these have been typically pursued on a project by project basis without any attempt to do this for a network wide objective. Some data pooling projects have also occurred without an exhaustive effort to ensure that all data available was included in the meta analysis. More importantly, there is no insurance that the data are being maintained in a reasonable electronic format beyond the time they are reported. The data are a valuable resource. The utility of such data beyond their original intended purpose is being appreciated particularly in the design of subsequent, prospective studies in similar populations. In addition, much of the PPRU-generated data are embedded in product labels or drug monographs. Such data are often used to drive dosing guidance, warnings and/or contraindications. Likewise, a more comprehensive strategy to house, maintain and provide access to this data is warranted.

This white paper discusses the project scope and functional requirements for a PPRU Clinical Data Repository (PeDaR). The repository will consist of a data warehouse maintained by the Network Coordinating Center (CC) with a user interface for downloading into analytic platforms. One such platform, iClinical, is designed for member access to data once compliance/permissions are established. PeDaR will contain not only PK data but will also house data generated from Network-affiliated studies regardless of study design or objectives. Thus, the repository can be used to:

- house study-related data from PPRU-affiliated trials
- index and join PK, PD, PK/PD and relevant PG data for across agent, therapeutic class and patient population
- create a data mart of PK, PD, PK/PD and relevant PG data that can be accessed and queried by PPRU CDR members
- index and join demographic and physiologic parameters for patients participating in PPRU trials
- create a data mart of demographic and physiologic parameter data that can be accessed and queried by PPRU PeDaR members

Other uses will certainly be defined and should be prioritized as they will impact the final functional requirements that define the IT effort.

PROJECT SCOPE

The project scope will address the following:

- Define and adopt standard data dictionaries for the definition of clinical, PK, PK/PD data, protocol/study elements etc to be stored in the PPRU data repository
- Define the process for identifying data to be collected and stored by CC into the PeDaR.
- Define the process for assigning rules / permissions on data access, within and across studies in the PPRU repository.
- Define requirements for the analytical interface to allow investigators to view, select and abstract data from the repository.

FUNCTIONAL REQUIREMENTS

Assuming the PPRU investigators support and agree with the PeDaR, the development of formal project requirements will proceed. Requirements will focus on the development of procedures to ensure the seamless registration of studies to the PeDaR and the details of accessibility and governance.

Development of standard data dictionaries is underway as is the development of common data collection forms. These are essential first steps in the workflow to be formalized upon broader acceptance of this proposal.

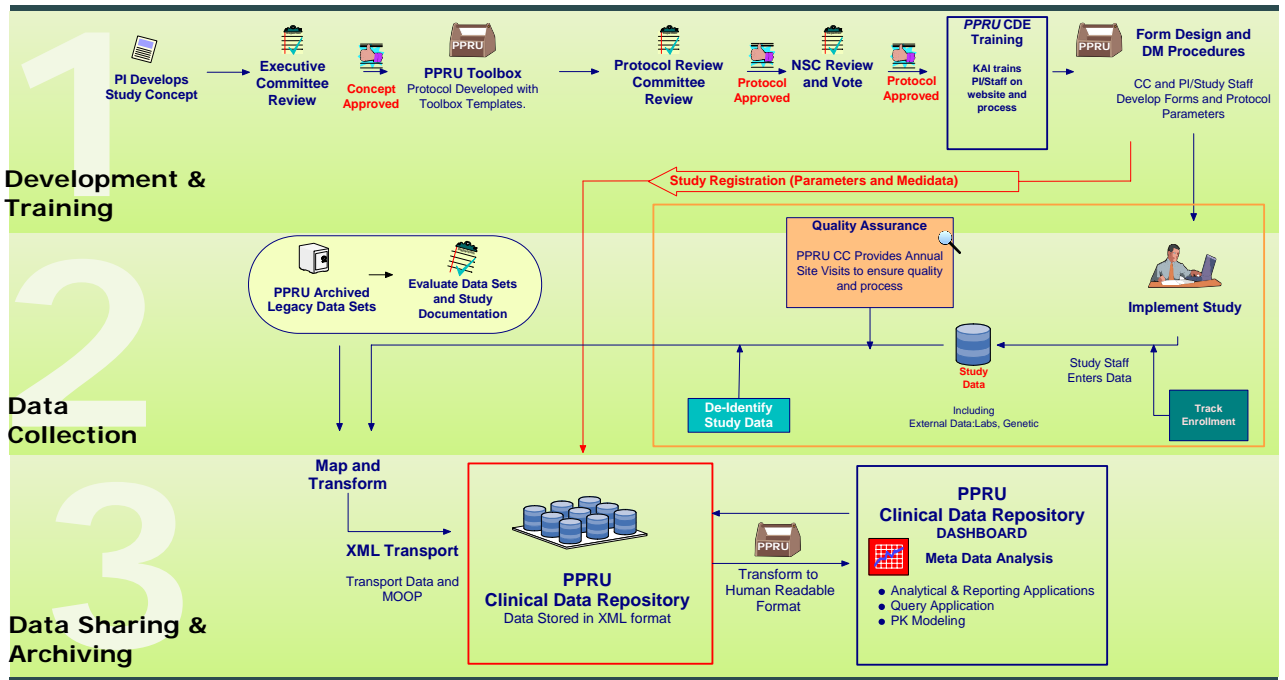
ACCESS and GOVERNANCE

Given the previous concerns around privacy, intellectual property and industry consent, much of the initial effort for the PeDaR project will be focused on detailing proposals for access and governance. As the initial effort will be focused on current and future studies, it is proposed that the PPRU craft language around the requirements of PeDaR to fulfill its commitment to the NIH data sharing policy and communicate this prospectively when dealing with industrial sponsors. Likewise, initially PeDaR will reflect the current PPRU data stakeholders so language on the privileges, access and accountability extended to PPRU sites and investigators will be defined in an agreement to be signed by those participating in the PeDaR creation. It should be appreciated by all that this may be a requirement in future RFPs of the PPRU.

Once the protocol is approved, the Coordinating Center will define the study template for the data warehouse. After study completion, access rights to the data will be determined and assigned.

Based on each investigator's profile and the definition of study stakeholder status and privileges, access to data will be provided. Likewise, access to completed and /or historical data can be petitioned to the PPRU CDR Committee (to be designated) so that meta-data can be assembled for further analysis. These details will be captured in the PeDaR agreement that all participants would ultimately agree to and sign.

PPRU Clinical Data Repository (CDR) Pathway



APPENDIX A: Timeline

Activity	Start Date	End Date
PPRU Meeting - White Paper, Proposed, Review and Comment	1/25/2008	2/1/2008
Discuss "Users" for iClinical development	1/25/2008	2/28/2008
Demo of iClinical for Pharmacometrics	2/1/2008	2/8/2008
Develop Governance and Data Sharing Policies	2/1/2008	3/30/2008
Establish Subcommittee and Develop Policy	1/25/2008	2/28/2008
Circulate and Revise Policies	3/1/2008	4/1/2008
Core Forms & Commons; Data Elements Finalized	11/1/2007	2/28/2008
Documents Finalized	4/2/2008	4/30/2008

Appendix G

List of Patient Oriented Publications

Patient-Oriented Therapeutics Publications

Abdel-Rahman SM, Benziger DP, Jacobs RF, **Jafri HS**, Fischer-Hong E, **Kearns GL**. Single-dose pharmacokinetics of daptomycin in children with suspected or proved Gram-positive infections. *Pediatr Infect Dis J* 2008 (April).

Abdel-Rahman SM, Jacobs RF, Massarella J, Kauffman RE, Bradley JS, Kimko HC, **Kearns GL**, Shalayda K, Curtin C, Maldonado SD, **Blumer JL**. Single-Dose Pharmacokinetics of Intravenous Itraconazole and Hydroxypropyl- β -Cyclodextrin in Infants, Children and Adolescents. *Antimicrobial Agents and Chemotherapy*, 2007 May 21.

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Hogg RJ, Delucchi A, Sakihara G, **Wells TG**, Tenney F, Batsky DL, **Blumer JL**, Vogt BA, Lo MW, Hand E, Panebianco D, Rippley R, Shaw W, Shahinfar S., A multicenter study of the pharmacokinetics of lisinopril in pediatric patients with hypertension. *Pediatric Nephrology*, 2007 May; 22(5):695-701.

James LP, Simpson PM, Farrar HC, **Kearns GL**, Wasserman GS, **Blumer J**, **Reed MD**, **Sullivan JE**, Hinson JA, (The Pediatric Pharmacology Research Unit Network, NICHD) Cytokines and toxicity in acetaminophen overdose. *J Clin Pharmacol*, 2005;45: (10): 1165-1171.

Jeha S, Gaynon PS, Razzouk BI, Franklin J, Kadota R, Shen V, Luchtman-Jones L, Rytting M, **Bomgaars LR**, Rheingold S, Ritchey K, Albano E, Arceci RJ, Goldman S, Griffin T, Altman A, Gordon B, Steinherz L, Weitman S, Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *Journal of Clinical Oncology*. April 2006; 24(12): 1917-1923. **PPRU Protocol # 10614, 10612.**

Kennedy MJ, Davis DA, Smith NB, Pierce WM, Pearce RE, **Gaedigk A**, **Kearns GL**. Growth Hormone Has No Effect on Activities of CYP1A2, N-acetyltransferase 2, Xanthine Oxidase or CYP2D6 in Children with Idiopathic Growth Hormone Deficiency. Submitted for publication

Kennedy MJ, Griffin AR, Su R, Merchant M., Klein JB. Urine collected from diapers can be used for proteomic profiling in infants and young children. Submitted for publication

Muller AE, de Jongh J, Bult Y, Goessens WH, Mouton JW, Danhof M, **van den Anker JN**. Pharmacokinetics of penicillin G in infants with a gestational age of less than 32 weeks. *Antimicrob Agents Chemother* 2007 Oct; 51(10):3720-5. Epub 2007 Jul 23.

Rakhmanina NY, Capparelli E, van den Anker JN, et al. Nevirapine concentration in non-stimulated saliva: an excellent substitute for plasma sampling in children with HIV-I infection. *Ther Drug Monitor* 2007;29:110-117.

Saez_Llorens X, Moreno MT, Ramilo O, **Sanchez PJ**, Top FH, Connor EM. Safety and pharmacokinetics of palivizumab therapy in children hospitalized with respiratory syncytial virus infection. *Pediatric Infectious Disease Journal*. 2004; 23: 707-712.

Sood BG, Delaney-Black V, Glibetic M, Aranda JV, Chen X, Shankaran S. PGE2/TXB2 imbalance in neonatal hypoxemic respiratory failure. *Acta Paediatrica*, 2007 May;96(5):669-73.

Toltzis P, Dul M, O'Riordan MA, Toltzis H, **Blumer JL**. Comparative effects of single-dose ceftriaxone versus three oral antibiotic regimens on stool colonization by resistant bacilli in children. *Pediatric Infectious Disease Journal*, 2007 Jan; 26(1):25-30.

Tutag Lehr V, Cepeda E, Frattarelli DAC, Thomas R, Whitty JE, Aranda JV. Lidocaine 4% cream (L.M.X.4) for anesthesia during newborn circumcision. *Obstetrics & Gynecology*. 2004; 103(4): S37. PPRU Protocol # 10522.

Walsh TJ, **Adamson PC**, Seibel NL, Flynn PM, Neely MN, Schwartz C, Shad A, Kaplan SL, Roden MM, Stone JA, Miller A, Bradshaw SK, Li SX, Sable CA, Kartsonis NA. An open-label, sequential dose-escalation study to investigate the pharmacokinetics, safety, and tolerability of Caspofungin in children and adolescents. *Antimicrobial Agents and Chemotherapy*. 2005 Nov; 49(11):4536-45.

Walsh TJ, Karlsson MO, Driscoll T, Arguedas AG, **Adamson P**, Saez-Llorens X, Vora AJ, Arrieta AC, **Blumer J**, Luster I, Milligan P, Wood N. Pharmacokinetics and safety of intravenous voriconazole in children after single or multiple-dose administration. *Antimicrobial Agents and Chemotherapy*. 2004; 48(6): 2166-2172.

Ward RM, Benitz WE, **Benjamin DK Jr**, Blackmon L, Giacoia GP, Hudak M, Lasky T, Rodriguez W, Selen A. Criteria supporting the study of drugs in the newborn. *Clinical therapeutics*, 2006 Sep;28(9):1385-98.

Ward RM, Kauffman R. Future of pediatric therapeutics: reauthorization of BPCA and PREA. *Clin Pharmacol Ther*, 2007 Apr;81(4):477-9.

Wenning LA, Murphy GM, James LP, Blumer JL, Marshall JD, Baier J, Scheimann AO, Panebianco DL, Zhong L, Eisenhandler R, Yeh KC, **Kearns GL**. Pharmacokinetics of famotidine in infants. *Clin Pharmacokinet* 2005; 44(3): 395-406.

Zuppa AF, Nicolson SC, **Adamson PC**, Wernovsky G, Mondick JT, Burnham N, Hoffman TM, Gaynor JW, Davis LA, Greeley WJ, Spray TL, **Barrett JS**. Population pharmacokinetics of milrinone in neonates with hypoplastic left heart syndrome undergoing stage I reconstruction. *Anesthesia and Analgesia*. April 2006; 102(4): 1062-1069. **PPRU Protocol # MSCIDA.**

Zuppa AF, Nadkarni V, Davis L, **Adamson PC**, Helfaer MA, Elliott MR, Abrams J, Durbin D. The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. *Critical Care Medicine*. 2004; 32(11): 2318-2322.

Appendix H

List of Publications in Neonatology

PPRU Network Publications Involving Neonatology 1994 to 2008

Neonatal Publications 1994-1998

Belsha CW, **Wells TG**, McNiece KL, et al. Pharmacokinetics and Pharmacodynamics of ranitidine in neonates treated with ECMO. *American Journal of Hypertension* 1998; 11:410-417

Kearns GL, van den Anker JN, Reed MD, Blumer JL. Pharmacokinetics of metoclopramide in neonates. *J Clin Pharmacol* 1998; 37:122-128

Mirochnick M, **Capparelli E**, Dankner W, et al. Zidovudine pharmacokinetics in premature infants exposed to HIV, *Antimicrob Agents and Chemother* 1998;42:808-812.

Neonatal Publications 1999-2003

Capparelli EV, Lane JR, Romanowski GL, et al. The influences of renal function and maturation on vancomycin elimination in newborns and infants. *Journal of Clin Pharmacol* 2001; 41:927-934.

Capparelli EV, Mirochnick M, Dankner W, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *Journal of Pediatrics* 2002; 47-52.

De Hoog M, Mouton JW, Schoemaker RC, Verduin CM, **van den Anker JN**. Extended interval dosing of tobramycin in neonates; implications for therapeutic drug monitoring. *Clin Pharmacol & Therapeutics* 2002; 71(5):349-358.

De Hoog M, Schoemaker RC, Mouton JW, **van den Anker JN**. Vancomycin population pharmacokinetics in neonates. *Clin Pharmacol & Therapeutics* 2000; 67:360-367.

De Wildt SN, **Kearns GL, Leeder JS, van den Anker JN**. Glucuronidation in humans. Pharmacogenetic and developmental aspects. *Clin Pharmacokinet* 1999; 36(6):439-452

De Wildt SN, **Kearns GL, Leeder JS, van den Anker JN**. Cytochrome P450 3A: ontogeny and drug disposition. *Clin Pharmacokinet* 1999; 37(6):485-505

De Wildt SN, Kerkvliet CT, Wezenberg MG, Ottink S, Hop WC, Vulto AG, **van den Anker JN**. Use of saliva in therapeutic drug monitoring of caffeine in preterm infants. *Therapeutic Drug Monitor* 2001; 23(3):250-254.

De Wildt SN, **Kearns GL**. Hop WC, Murry DJ, Abdel-Rahman SM, **van den Anker JN**. Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. *Clin Pharmacol & Therapeutics* 2001; 70(6):525-531.

De Wildt SN, **Kearns GL**, Hop WC, Murry DJ, Abdel-Rahman SM, **van den Anker JN**. Pharmacokinetics and metabolism of oral midazolam in preterm infants. *British Journal of Clin Pharmacol* 2002; 53(4):390-392.

Helms RA, Storm MC, Stuck KL, et al. A Phase I open-label study of the safety and pharmacokinetics of repeated-dose micafungin in neonates. *Journal of Pediatrics* 1999; 134(3):358-361.

Kearns GL, Bradley JS, Jacobs RF, et al. Single dose pharmacokinetics of pleconaril in neonates. *Ped Infect Dis J* 2000; 19:833-839.

Kearns GL, Jungbluth GL, Abdel-Rahman SM, Hopkins NK, Welshman IR, Grzebyk RP, Bruss JB, **van den Anker JN**. Impact of ontogeny on linezolid disposition in neonates and infants. *Clin Pharmacol Ther* 2003; 74(5):413-422.

Kearns GL, Robinson PK, Wilson JT, Costello D, Ward RM, **van den Anker JN**. Cisapride disposition in neonates and infants: in vivo relection of cytochrome P450 3A4 ontogeny. *Clin Pharmacol Ther* 2003; 74(4):312-325.

Monin P, **Aranda J**, Bansal K, Trippenbach T. Effect of increased GABA concentrations on breathing in unanesthetized newborn rabbits. *Biology of the Neonate* 1999; 76(3):168-180.

Van Overmeire B, Touw D, Schepens PJ, **Kearns GL**, **van den Anker JN**. Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. *Clin Pharmacol & Therapeutics* 2001; 70:336-343.

Neonatal Publications 2004-Present

Acosta EP, Brundage RC, King JR, **Sanchez PJ**, et al. Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid valganciclovir formulation. *Clin Pharmacol & Therapeutics* 2007; 81(6):867-872.

Allegaert K, Anderson BJ, **van den Anker JN**, et al. Renal drug clearance in preterm neonates: relation to prenatal growth. *Therapeutic Drug Monitoring* 2007;29(3):284-291.

Allegaert K, van Schaik RH, Vermeersch S, Verbesselt R, Cossey V, Vanhole C, van Fessem M, de Hoon J, **van den Anker JN**. Postmenstrual age and CYP2D6 polymorphisms determine tramadol O-demethylation in critically ill neonates and infants. *Pediatric Research* 2008.

Anderson BJ, Allegaert K, **van den Anker JN**, et al. Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance. *British J Clin Pharmacol* 2007; 63(1):75-84.

Aranda JV, Cataldi L, Fanos V. Clinical pharmacology of antimicrobials for urinary tract infections in newborns and young infants. *J Chemother* 2006; 18(3):14-15.

Frattarelli DA, Ergun H, Lulic-Botica M, **Aranda JV**. Vancomycin elimination in human infants with intrauterine growth retardation. *Pediatr Infect Dis J* 2005; 24(11):979-983.

Beharry KD, Modanlou HD, **Hasan J**, et al. Comparative effects of early postnatal ibuprofen and indomethacin on VEGF, IGF-1, and GH during rat ocular development. *Invest Ophthalmol* 2006; 47(7):3036-3043.

Blake MJ, Abdel-Rahman SM, Pearce RE, Leeder JS, **Kearns GL**. Effect of diet on the development of drug metabolism by cytochrome P-450 enzymes in healthy infants. *Pediatr Res* 2006; 60(6):717-723.

Blake MJ, Gaedigk A, Pearce RE, Bomgaars LR, Christensen ML, Stowe C, James LP, Wilson JT, **Kearns GL**, Leeder JS. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. *Clin Pharmacol & Therapeutics* 2007; 81(4):510-516.

Capparelli E, Hochwald C, Rasmussen M, et al. Population pharmacokinetics of cefepime in the neonate. *Antimicrob Agents & Chemother* 2005; 49:2760-2766.

De Wildt SN, Berns MJ, **van den Anker JN**. ¹³C-erythromycin breath test as a noninvasive measure of CYP3A activity in newborn infants: a pilot study. *Therapeutic Drug Monitoring* 2007; 29(2):225-230.

Finkel JC, Quezado ZM. Hypothermia-induced bradycardia in a neonate receiving dexmedetomidine. *J Clin Anesth* 2007; 19(4):290-292.

Finkel JC. Use of nonsteroidal anti inflammatory drugs in preterm, term neonates and infants: analgesia by consensus? *Paed Anesth* 2007; 17(10):915-917.

Galinkin JL, Kurth CD, Shi H, Priestly MA, Loepke AW, **Adamson PC**. The plasma pharmacokinetics and cerebral spinal fluid penetration of intravenous topiramate in newborn pigs. *Biopharm Drug Dispos* 2004; 25(6):265-271.

Keller RL, Tacy TA, Fields S, Ofenstein JP, **Aranda JV**, Clyman RI. Combined treatment with a nonselective nitric oxide synthase inhibitor (l-NMMA) and indomethacin increases ductus constriction in extremely premature newborns. *Pediatr Res* 2005; 58(6):1216-1221.

Kovacs A, Cowles MK, Britto P, **Capparelli E**, et al. Pharmacokinetics of didanosine and drug resistance mutations in infants exposed to ZDV during gestation or postnatally and treated with didanosine and zidovudine in the first three months of life. *Ped Infect Dis J* 2005; 24:503-509.

Heresi GP, Gerstmann DR, **Reed MD, van den Anker JN, Blumer JL**, Kovanda L, Keirns JJ, Buell DN, **Kearns GL**. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. *Ped Infect Dis J* 2006; 25(12):1110-1115.

Lehr VT, Cepeda E, Frattarelli DA, Thomas R, LaMothe J, **Aranda JV**. Lidocaine 4% cream compared with lidocaine 2.5% and prilocaine 2.5% or dorsal penile block for circumcision. *Am J Perinatol* 2005; 22(5):231-237.

Lehr VT, Zeskind PS, Ofenstein JP, Cepeda E, Warriar I, **Aranda JV**. Neonatal facial coding system scores and spectral characteristics of infant crying during newborn circumcision. *Clin J Pain* 2007; 23(5):417-424.

Lugo RA, Ballard J. Albuterol delivery from MDI and spacer is reduced following short duration manual ventilation in a neonatal ventilator-lung model. *Respiratory Care* 2004; 49(9):1029-1034.

Madadi P, Koren G, Cairns J, Chitayat D, Gaedigk A, **Leeder JS**, et al. Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician* 2007; 53(6):33-35.

Mirochnick M, Stek A, Acevedo M, Keller M, Holland D, **Capparelli E**, et al. Safety and pharmacokinetics of nelfinavir co-administered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquired Immune Deficiency Syndromes* 2005; 39:189-194.

Muller Ae, De Jongh J, Bult Y, Goessens WH, Mouton JW, Danhof M, **van den Anker JN**. Pharmacokinetics of penicillin G in infants with a gestational age of less than 32 weeks. *Antimicrob Agents & Chemother* 2007; 51(10):3720-3725.

Shapiro R, Holland D, **Capparelli E**, et al. HIV inhibitory serum concentrations of antiretrovirals detected in breastfeeding infants of women receiving antiretroviral treatment in Botswana. *JID* 2005; 192:720-727.

Shellhaas R, **Clancy R**. Contemporary characterization of neonatal seizures by full array and single channel EEGs. *J Clin Neurophysiol* 2007; 118:2156-2161.

Shellhaas R, Soaita A, **Clancy RR**. The sensitivity of amplitude-EEG in neonatal seizure detection. *Pediatrics* 2007; 120:770-777.

Sood BG, Glibetic B, **Aranda JV**, et al. Systemic levels following PGE1 inhalation in neonatal hypoxemic respiratory failure. *Acta Paediatr* 2006; 95(9):1093-1098.

Van Woerkom R, Beharry KD, Mondanlou HD, Parker J, Rajan V, Akmal Y, **Aranda JV**. Influence of morphine and naloxone on endothelin and its receptors in newborn piglet brain vascular endothelial cells: clinical implications in neonatal care. *Pediatr Res* 2004; 55(1):147-151.

Appendix I

Trainee Publications and Career Progression

Trainee Publications and Career Progression (all trainees are in bold)

1995

Wu LR, Capparelli EV, Connor JD. Therapy of pediatric AIDS. *Curr Opin Pediatr* 1995; 7:214-9.

1996

James LP, Marshall JD, Heulitt MJ, Wells TG, Letzig L, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in children. *Journal of Clinical Pharmacology* 1996; 36:48-54.

1998

James LP, Farrar HC, Komoroski EM, Wood WR, Graham CJ, Bornemeier RA, Valentine JL. Sympathomimetic drug use in adolescents presenting to a pediatric emergency department with chest pain. *Clinical Toxicology* 1998; 36(4):321-328.

James LP, Marotti T, Stowe CD, Farrar HC, Taylor BJ, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in infants. *Journal of Clinical Pharmacology* 1998; 38:1089-1095.

Mirochnick M, Capparelli E, Dankner W, Sperling RS, Van Dyke R, Spector S. Zidovudine pharmacokinetics in premature infants exposed to HIV. *Antimicrob Agent Chemother* 1998; 42:808-812.

Schexnayder S, **James LP**, Kearns GL, Farrar HC. The pharmacokinetics of continuous infusion pralidoxime in children with organophosphate poisoning. *Clinical Toxicology* 1998; 36(6):459-555.

1999

Farrar HC, **James LP**. Characteristics of pediatric admissions for cyclic antidepressant poisoning. *American Journal of Emergency Medicine* 1999; 17(5):495-496.

James LP, Stowe CD, Farrar HC, Menendez AA, Argao EA. The pharmacokinetics of oral ranitidine in children and adolescents with cystic fibrosis. *Journal of Clinical Pharmacology* 1999; 39:1242-1247.

Kearns GL, Abdel-Rahman SM, **James LP**, Blowey DL, **Marshall JD**, Wells TG, Jacobs RF and the Pediatric Pharmacology Research Unit Network. Single-dose pharmacokinetics of a pleconaril (VP63843) oral solution in children and adolescents. *Antimicrobial Agents and Chemotherapy*, 1999; 43(3):634-638.

Marshall JD, Kearns GL. Developmental pharmacodynamics of cyclosporine. *Clin Pharm Ther* 1999; 66:66-75.

Mirochnick M, **Capparelli EV**, **Connor JD**. **Pharmacokinetics of zidovudine in infants: a population analysis across studies. Clin Pharmacol Therap 1999; 66:16-24.**

2000

Alander SW, Dowd MD, Bratton SL, Kearns GL. Pediatric acetaminophen overdose: risk factors associated with hepatocellular injury. *Arch Pediatr Adolesc Med*. 2000; 154: 346-350.

Glauser TA, Nigro M, Sachdeo R, Pasteris LA, Weinstein S, Abou-Khalil B, et al. Adjunctive therapy with oxcarbazepine in children with partial seizures. The Oxcarbazepine Pediatric Study Group. *Neurology* 2000; 54(12):2237-44.

Glauser TA, Pippenger CE. Controversies in blood-level monitoring: reexamining its role in the treatment of epilepsy. *Epilepsia* 2000; 41 Suppl 8:S6-15.

Glauser TA. Topiramate in the catastrophic epilepsies of childhood. *J Child Neurol* 2000; 15 Suppl 1:S14-21.

Schutze GE, **Lowry JA**, Kearns GL. Monitoring of aminoglycoside serum concentrations. *Pediatr Infect Dis J*. 2000; May: 489-490.

Williams KM, Kearns GL. Lipid amphotericin preparations. *Pediatr Infect Dis J*. 2000; 19: 567-569.

2001

Behm MO, Kearns GL. Treatment of pain with gabapentin in a neonate. *Pediatrics*. 2001; 108: 482-484.

Berg S, Serabe B, Aleksic A, **Bomgaars L**, McGuffey L, Dauser R, Durfee J, Nuchtern J, Blaney S. Pharmacokinetics and cerebrospinal fluid penetration of phenylacetate and phenylbutyrate in the nonhuman primate. *Cancer Chemotherapy and Pharmacology*. May 2001; 47(5): 385-390.

Evans WE, Hon YY, **Bomgaars L**, Coutre S, Holdsworth M, Janco R, Johnson R, Kalwinsky D, Keller F, Khatib Z, Margolin J, Murray J, Quinn J, Ravindranath Y, Ritchey K, Roberts W, Rogers Z, Schiff D, Steuber C, Tucci F, Kornegay N, Krynetski EY, Relling M. Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine or azathioprine. *J. Clin. Oncology*. April 2001; 19(8): 2293-2301.

Lowry JA, Jarrett RV, Wasserman G, Pettett G, Kauffman RE. Theophylline toxicokinetics in premature newborns. *Archives of Pediatrics and Adolescent Medicine*. 2001: 934-939.

Lowry JA, Corry A, Fitzmaurice L, Jackson MA, Kearns GL. Coadministration of mefloquine and chloroquine: use of a pharmacokinetic based approach to reduce toxicity. *Pediatric Infectious Disease Journal*. 2001; 20: 223-224.

2002

Aravind MK, **Precilla R**, Ofenstein JP. A rapid and sensitive high-performance liquid chromatography assay of rofecoxib in human serum. *Journal of Chromatographic Science*. 2002 Jan; 40(1):26-8. **PPRU Protocol # 10300**.

Glauser TA, Pellock JM. Zonisamide in pediatric epilepsy: review of the Japanese experience. *J Child Neurol* 2002; 17(2):87-96.

Lacayo NJ, Lum BL, Becton DL, Weinstein H, Ravindranath Y, Chang MN, **Bomgaars LR**, Lauer SJ, Sikic BI, Dahl GV. Pharmacokinetic interactions of cyclosporine with etoposide and mitoxantrone in children with acute myeloid leukemia. *Leukemia* 2002; 16(5): 920-927.

Ostrea EM, Morales V, Ngoumgna E, **Precilla R**, Tan E, Hernandez E, Ramirez GB, Cifra HL, Manlapaz ML. Prevalence of fetal exposure to environmental toxins as determined by meconium analysis. *Neurotoxicology*. 2002 Sep; 23(3):329-39.

2003

Behm MO, Kearns GL. Crotaline Fab antivenom for treatment of children with rattlesnake envenomation. *Pediatrics*. 2003; 112: 1458-1459; author reply 1458-1459.

Best BM, Burns JC, DeVincenzo J, Phelps SJ, Blumer JL, Wilson JT, Capparelli EV, Connor JD and the Pediatric Pharmacology Research Unit Network Pharmacokinetic Safety Evaluation of a Pediatric Oral Formulation of Pentoxifylline in Kawasaki Disease. *Curr Ther Res Clin Exp*. 2003; 64:96-115.

Kearns GL, Abdel-Rahman SM, **Alander SW**, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003; 349: 1157-1167.

Kearns GL, Heacock J, Daly SJ, Singh H, **Alander SW**, Qu S. Percutaneous lidocaine administration via a new iontophoresis system in children: tolerability and absence of systemic bioavailability. *Pediatrics*. 2003; 112: 578-582.

Lowry JA, Kearns GL, Abdel-Rahman SM, Nafziger AN, Khan IS, Kashuba AD, Schuetz EG, Bertino JS Jr, van den Anker JN, Leeder JS. Cisapride: a potential model substrate to assess cytochrome P4503A4 activity in vivo. *Clin Pharmacol Ther*. 2003; 73: 209-222.

Lulic M, **Ergun H**, **Frattarelli DAC**, Tutag Lehr V, Aranda JV. Vancomycin Elimination in Intrauterine Growth Retardation. *Pediatric Research*. 2003; 53(4): 317A.

Maples HD, Stowe CD, Saccente SL, Jacobs RF. Voriconazole serum concentration in an infant treated for *Trichosporon beigeli* infection. *Pediatric Infectious Disease Journal*. 2003; 22(11):1022-4.

Maples HD, James LP, Stowe CD, Jones DP, Hak EB, Blumer JL, Vogt B, Wilson JT, Kearns GL, Wells TG. Famotidine Disposition in Children and Adolescents with Chronic Renal Insufficiency. *Journal of Clinical Pharmacology* 2003; 43(1):7-14.

Sandhu RS, **Precilla RP**, Simonelli TM, Edwards DJ. Influence of goldenseal root on the pharmacokinetics of indinavir. *Journal of Clinical Pharmacology*. 2003; 43: 1283-1288

Thompson P, Balis F, Serabe BM, Berg S, Adamson P, Klenke R, Aiken A, Packer R, Murry DJ, Jakacki R, Blaney SM. Pharmacokinetics of phenylacetate administered as a 30-min infusion in children with refractory cancer. *Cancer Chemotherapy and Pharmacology*. Nov. 2003; 52(5): 417-423.

2004

Abdel-Rahman SM, Penny J, **Alander SW**. Trichophyton rubrum tinea capitis in a young child. *Pediatr Dermatol*. 2004; 21: 63-65.

Bomgaars LR, Geyer JR, Franklin J, Dahl G, Park J, Winick NJ, Klenke R, Berg SL, Blaney SM. Phase I trial of Intrathecal Liposomal Cytarabine in Children with Neoplastic Meningitis. *Journal of Clinical Oncology*. 2004; 22: 3916-3921.

Chintagumpala M, Blaney SM, **Bomgaars LR**, Aleksic A, Kuttesch JF, Klenke RA, Berg SL. Phase I and pharmacokinetic study of thalidomide with Carboplatin in children with cancer. *Journal of Clinical Oncology*. Nov 2004; 22(21): 4394-4400.

Cohen IT, **Finkel JC**, Hannallah RS, Goodale DB. Clinical and biochemical effects of propofol versus sevoflurane in healthy infants and young children. *Paediatric Anaesthesia* 2004; 14:135-42.

Ergun H, Frattarelli DA, Aranda JV. Characterization of the role of physiochemical factors on the hydrolysis of dipyrrone. *Journal of Pharmaceutical and Biomedical Analysis*. May 2004; 35(3): 479-487.

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Karen Dineen Wagner, **Adelaide S. Robb**, Robert L. Findling, Jianqing Jin, Marcelo M. Gutierrez, and William E. Heydorn. A Randomized, Placebo-Controlled Trial of Citalopram for the Treatment of Major Depression in Children and Adolescents *Am J Psychiatry*, Jun 2004; 161: 1079 - 1083.

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Kennedy MJ, Abel-Rahman SM, Simon SD, Leeder JS. Comparison of various urine collection intervals for caffeine and dextromethorphan phenotyping in children. *Journal of Clinical Pharmacology*. 2004; 44: 708-714.

Kennedy MJ, Jackson MA, Myers AL, Williams KM, Kearns GL. Sub-optimal antimicrobial exposure as a potential cause of treatment failure following single-dose amoxicillin prophylaxis in a child. *Clinical Pediatrics*. 2004; 43: 773-776.

Kennedy MJ, Abdel-Rahman SM, Kearns GL, Jungbluth GL. Evaluating pharmacodynamic surrogates in response to the treatment of skin and skin structure infections in children. *Paediatric and Perinatal Pharmacology*. 2004; 6: 32-37.

Lee WE, Lugo RA, Rusho WJ, MacKay M. Stability of extemporaneously prepared lorazepam suspension at two temperatures. *J Pediatr Pharmacol Ther* 2004; 9:254-258.
trainee

Neville K, Blaney S, Bernstein M, **Thompson P**, Adams D, Aleksic A, Berg S. Pharmacokinetics of O-6-benzylguanine (O-6BG) in pediatric patients with central nervous systems tumors: a Pediatric Oncology Group Study. *Clinical Cancer Research*. Aug 2004; 10(15): 5072-5075.

Neville K, Thompson P, Parise RA, Aleksic A, Egorin M, Balis F, McGuffey L, McCully C, Berg S, Blaney S. Plasma and CSF pharmacokinetics of imatinib after intravenous and oral administration in nonhuman primates. *Clinical Cancer Research*. 2004; 10(7): 2525-2529.

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Rakhmanina N, van den Anker JN, Soldin S. Safety and pharmacokinetics of antiretroviral therapy during pregnancy. *Ther Drug Monitor* 2004; 26(2):110-5.

Silber TJ, **Robb AS**, Orrell-Valente JK, Ellis N, Valadez-Meltzer A, Dadson MJ. Nocturnal nasogastric refeeding for hospitalized adolescent boys with anorexia nervosa. *J Dev Behav Pediatr*. 2004 Dec; 25(6):415-8.

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Pediatric Clinical Pharmacology Trainees at PPRU sites since 1994

Site	Name	Dates of training	Description of Training	Title or Position / Institution	Special honors/ recognition	Current Professional Leadership Roles in Clinical Pharmacology
Arkansas	Laura James, MD	1994-1996	Pediatric Clinical Pharmacology Fellow; Associate Clinical Pharmacologist	PI for the Arkansas PPRU.	R03, R01, STTR grant recipient, Diplomat ABCP	Associate Editor, Clinical Pharmacology and Therapeutics
Arkansas	Jim Marshall, MD	1994-1996	Pediatric Clinical Pharmacology Fellow; Associate Clinical Pharm	Cook Children's Hosp. TX	Diplomat ABCP	
Arkansas	Cindy Stowe, PharmD	1996-1998	Associate Clinical Pharmacologist	Associate Dean, UAMS School of Pharmacy		
Arkansas	Holly Maples, PharmD	2001-2003	Pediatric Clinical Pharmacology Fellow; Associate Clinical Pharm	UAMS School of Pharmacy; Arkansas Children's Hospital		
Arkansas	Brian Donahower	2004-2007	Pharmacology graduate student	Research associate, UAMS Cancer Institute		
Arkansas	Catherine O'Brian, PharmD	2008-Current	Associate Clinical Pharmacologist	Associate Clinical Pharmacologist		
Baylor	Lisa Bomgaars, MD	1999-2000	PPRU Associate Clinical Pharmacologist	Associate PI for Baylor; PPRU Assistant Professor of Pediatrics,	Diplomate, American Board of Clinical Pharmacology	Chair, ASCPT Education Committee
Baylor	Kathleen Neville, MD	2001-2002	MSCIDA fellow	Assistant Professor of Pediatrics Divisions of Hematology/Oncology and Clinical Pharmacology and Medical Toxicology Children's Mercy Hospitals and Clinics Kansas City	K23 grant recipient (NHLBI); Diplomat of ABCP	Vice Chairman, ASCPT Education Committee
Baylor	Terza Horton, MD	2002-2004	Pharmacology postdoc	Assistant Professor Pediatrics BCM	K12 and K23 grant recipient (NCI)	COG, Young Investigator Committee
Baylor	Patrick Thompson, MD	2005-Current	MSCIDA fellow	Assistant Professor Pediatrics BCM	Diplomate, American Board of Clinical Pharmacology	
Baylor	Lindsay Kilburn, MD	2005-Current	T32 - BCM Training Research Program for Pediatrics; K12 Faculty Fellowship in Hematology-Oncology Clinical Pharmacology Research Track	Clinical Instructor Pediatrics BCM	Clinical Scholar Award; Diplomat American Board of Clinical Pharmacology	
Baylor	Emma Jones, M.D.	2007-Current	Clinical Pharmacology Fellow; T32- BCM Training Research Program for Pediatrics	Fellow Department of Pediatrics BCM	T32 Research Training Grant recipient	
Baylor	Patricia Baxter, M.D.	2007-Current	Clinical Pharmacology Fellow; T32 - BCM Training Research Program for Pediatrics	Fellow Department of Pediatrics BCM	T32 Research Training Grant recipient	
CHOP	Manish Gupta, PhD	2005-2007	Pharmacometrics Fellow - Pfizer Postdoc			Principal Scientist, Modeling & Simulation, Genentech Pharmaceuticals
CHOP	Divya Menon, PhD	2006-2008	Pharmacometrics Fellow - GSK Postdoc	CHOP Postdoc	ACCP New member award (2006); ACCP Postdoc award (2007)	Clinical Pharmacology Reviewer; US FDA
CHOP	John Mondick, PhD	2007- Current	Adjunct Clinical Pharmacologist	Assistant Professor, Pediatrics, U. Penn School of Medicine		
CHOP	Olivera Marsenic, MD	2007- Current	Clinical Pharmacology Fellow	Fellow, Nephrology		
CHOP	Robin Norris, MD	2007- Current	Clinical Pharmacology Fellow	Fellow, Department of Hematology/Oncology		
CHOP	Doug Marsteller, PhD	2008-Current	Pharmacometrics Fellow - Genentech Postdoc	CHOP Postdoc		
CHOP	Craig Comisar, PhD	2008-Current	Pharmacometrics Fellow - Pfizer Postdoc	CHOP Postdoc		
CHOP	Jeffrey Galinkin, MD	2001-2002	PPRU Associate Clinical Pharmacologist	Denver Children's		
CHOP	Amelia Walls, PhD	2003-2004	PPRU Associate Clinical Pharmacologist			
CHOP	Athena Zuppa, MD	2003-2004 2005-2006	MSCIDA fellow PPRU Associate Clinical Pharmacologist	CHOP PPRU	K 23 award recipient; Board Certified ABCP; ACCP Fellow	
CHOP	Jeff Skolnik, MD	2005-2006	Clinical Pharmacology Fellow	CHOP PPRU		Astra Zeneca Pharmaceuticals, Oncology
CHOP	Kelly Wade, MD, PhD	2006- Current	Adjunct Clinical Pharmacologist MSCIDA Fellow	CHOP PPRU	K 23 award recipient	
CHOP	Manish Gupta, PhD	2005-2007	Pharmacometrics Fellow - Pfizer Postdoc			Principal Scientist, Modeling & Simulation, Genentech Pharmaceuticals
CHOP	Divya Menon, PhD	2006-2008	Pharmacometrics Fellow - GSK Postdoc	CHOP Postdoc	ACCP New member award (2006); ACCP Postdoc award (2007)	Clinical Pharmacology Reviewer; US FDA
CHOP	John Mondick, PhD	2007- Current	Adjunct Clinical Pharmacologist	Assistant Professor, Pediatrics, U. Penn School of Medicine		
CHOP	Olivera Marsenic, MD	2007- Current	Clinical Pharmacology Fellow	Fellow, Nephrology		
CHOP	Robin Norris, MD	2007- Current	Clinical Pharmacology Fellow	Fellow, Department of Hematology/Oncology		
CHOP	Doug Marsteller, PhD	2008-Current	Pharmacometrics Fellow - Genentech Postdoc	CHOP Postdoc		
CHOP	Craig Comisar, PhD	2008-Current	Pharmacometrics Fellow - Pfizer Postdoc	CHOP Postdoc		
Cincinnati	Mark Solomon, MD	2000-2003	Clinical Pharmacology and Pediatric Clinical Trials; Supervised collaborative clinical trials initiated through the PPRU.	Private Practice, Pulmonary Medicine, Galveston, Texas		
Cincinnati	Tracy Glauser, MD	2000-2003	Clinical Pharmacology and Pharmacogenetics as part of K08 training.	Professor, Division of Neurology, Cincinnati Children's Hospital Medical Center		
Cincinnati	Diego Morita, MD	2002-present	Clinical Pharmacology and Pharmacogenetics and pharmacokinetic/pharmacodynamic modeling approaches to individualized therapy	Assistant Professor, Division of Neurology, Cincinnati Children's Hospital Medical Center		
Cincinnati	Ivana Kacirova, MD	2003-2004	Pediatric Clinical Trials and Therapeutic Drug Management	Assistant Professor, Ostrava University, Czech Republic		
Cincinnati	Parinda Mehta, MD	2004-2005	Ped Clin Pharmacology Fellow	Assistant Professor, Division of Hematology/Oncology; Cincinnati Children's Hospital Medical Center		
Cincinnati	Ahbi Shinde, MD	2004-2005	Clinical Pharmacology and Peds Clinical Trials	Fellow, Clinical Pharmacology University of Chicago		
Cincinnati	Reuven Schore, MD	2005-2006	Ped Clin Pharmacology Fellow; MSCIDA candidate	Fellow, Division of Hematology/Oncology; Cincinnati Children's Hospital Medical Center		

Site	Name	Dates of training	Description of Training	Title or Position / Institution	Special honors/ recognition	Current Professional Leadership Roles in Clinical Pharmacology
Cincinnati	Shannon Saldana, MD	2006-present	PPRU Associate Clinical Pharmacologist	Instructor of Pediatrics		
Cincinnati	Kristina Wiers, MD	2007-present	Population PK/PD modeling and simulation	Fellow, Rheumatology/PPRU		
Cincinnati	Stephanie Merhar, MD	2007-present	Phase I study design in neonates; Population PK/PD modeling and simulation	Fellow, Neonatology/PPRU		
Cleveland	Janice Sullivan, MD	1991 - 1995	Dual Peds Crit Care and Clin Pharm Fellowship	Professor, Pediatrics and Pharmacology/Toxicology, Univ Louisville; Kosair Children's Hospital PPRU PI		Vice Chair, Pediatric and Maternal Pharmacology Section, American Society for Clinical Pharmacology and Therapeutics; Executive Committee, Section on Clinical Pharmacology and Therapeutics, American Academy of Pediatrics
Cleveland	Mark Glover, PharmD	1994-1996	Peds Clin Pharmacology Fellow	Assoc Prof Nova SE Univ College of Pharmacy Ft Lauderdale FL		
Cleveland	Hidefumi Nakamura, MD	1996-1999	Ped Clin Pharmacology Fellow	Director Clin Research, Natl Ctr for Child Health and Development, Tokyo Japan		
Cleveland	Andrew TenEick, PharmD	1998 - 2000	Ped Clin Pharmacology Fellow	PICU Pharmacy Mgr, Children's Med Ctr of Dallas		
Cleveland	Michael Neely, MD	1999 - 2002	MSCIDA fellow and dual fellow in Peds ID	Asst Prof of Pediatrics, Keck School of Med, Univ S California		
Cleveland	Allison Chung, PharmD	2000 - 2002	Ped Clin Pharmacology Fellow	Asst Prof Pharmacy Practice, Auburn Univ, Harrison School of Pharmacy, Mobile AL		
Cleveland	Todd Kociancic, PharmD	2001 - 2003	Ped Clin Pharmacology Fellow	BCPS Clin Specialist, Crit Care Med, Rose Dominican Hospitals, Nevada		
Cleveland	Michelle Bestic, PharmD	2004 - 2006	Ped Clin Pharmacology Fellow	Instructor in Pediatrics, Case Western Res Univ, Cleve OH; Staff, Rainbow Babies & Children's Hospital, Cleve OH		
Cleveland	Martha Blackford, PharmD	2006-2007	Ped Clin Pharmacology Fellow	Left Rainbow Babies and Children's Hospital on 06/30/07 to complete fellowship at Akron Children's Hospital		
CNMC	Julia Finkel, MD	2004-2006	PPRU Adjunct Clinical Pharmacologist	Assoc PI CNMC PPRU; Assoc Professor Peds and Anesth	Vice Chair of Anesthesia and Pain Medicine at CNMC	
CNMC	Darbari, MD	2005-2007	Ped Clin Pharmacology Fellow	Ass Prof Peds George Washington Univ	Will start fellowship Pediatric Hematology/Oncology at Hopkins July 2008	
CNMC	Rakhmanina, MD	2008-now	PPRU Adjunct Clinical Pharmacologist	Ass Prof Peds George Washington Univ	Program Director HIV/AIDS at CNMC and currently funded through K-12 award	
CNMC	Best, MD	2005-2007	Ped Clin Pharmacology Fellow	Ass Prof Peds George Washington Univ	Has received several grants for her studies in passive smoking in African American children	
CNMC	Robb, MD	2006-2008	PPRU Adjunct Clinical Pharmacologist	Assoc Prof Peds George Washington Univ	Member AAP Committee on Drugs	
CNMC	Yewande Johnson, MD	2006-now	MSCIDA fellow	Ass Prof Peds George Washington Univ		
North Carolina	Brad Harris, MD	7/1/04 - 6/30/06	Clinical trials; K30 program Assistant Professor, UNC Department of Pediatrics	Assistant Professor of Pediatrics University of North Carolina		
North Carolina	Cassandra Moran, MD	7/1/04 - 6/30/06	Pharmacology postdoc	Instructor, Duke University		
North Carolina	Brian Smith MD	2006-2008	MPH Biostatistics with concentration in PK-PD	Assistant Professor Neonatology Duke University		
North Carolina	Micky Cohen-Wolkowicz, MD	2006-2009	PhD School of Pharmacy UNC	Fellow, Pediatric Infectious Disease Duke University		
North Carolina	Souzan Yanni	2006-2010	PhD School of Pharmacy UNC	Doctoral Student University of North Carolina		
Kansas City	Jennifer A. Lowry, M.D.	1999-2002	MSCIDA fellow, joint fellowship in Pediatric Clinical Pharmacology and Medical Toxicology	Assistant Professor of Pediatrics and Director, Regional Poison Control Ctr. University of Kansas School of Medicine, Kansas City, KS		
Kansas City	Mary Jayne Kennedy, Pharm.D.	2000-2002	Pediatric Clinical Pharmacology Fellow	Assistant Professor of Pediatrics and Pharmacology; Associate Director, Kosair Charities Pediatric Clinical Research Unit, University of Louisville and Kosair Children's Hospital, Louisville, KY	ASCPT President's Award	Invited Member, NHLBI Early Pseudomonas Infection Control (EPIC) Trial DSMB; Editorial Board: Journal of Pediatric Pharmacology and Therapeutics
Kansas City	Martin O. Behm, M.D.	2001-2004	Pediatric Clinical Pharmacology Fellow	Medical Director, Drug Safety McNeil Consumer Products Division, Johnson & Johnson Co., Inc.	ASCPT President's Award	
Kansas City	Kathy Williams, M.D.	2001-2003	Combined Infectious Disease and Clinical Pharmacology Fellowship	Private practice of Pediatrics London, England		
Kansas City	Sarah W. Alander, M.D.	2001-2003	Pediatric Clinical Pharmacology Fellowship	Dept. of Emergency Medicine St. John's Hospital, St. Louis, MO		
Kansas City	Michael J. Blake, M.D., Ph.D.	2002-2004	Pediatric Clinical Pharmacology Fellow	Private Pediatric Practice, Ottumwa, Iowa	ASCPT President's Award; Midwest SSPR Young Investigator's Award	
Kansas City	Lisa M. Castro, M.D.	2004 - 2005	Pediatric Clinical Pharmacology Fellowship	Assistant Professor of Pediatrics and member, Divisions of Neonatology and Pediatric Pharmacology & Medical Toxicology University of Missouri-Kansas City School of Medicine and Children's Mercy Hospitals and Clinics, Kansas City, MO		

Site	Name	Dates of training	Description of Training	Title or Position / Institution	Special honors/ recognition	Current Professional Leadership Roles in Clinical Pharmacology
Kansas City	Bridgette A. Jones, M.D.	August 2007 - present	Pediatric Clinical Pharmacology Fellowship	Asst. Clinical Professor in Pediatrics, Member, Division of Allergy/Asthma/Clinical Immunology, Children's Mercy Hospitals and Clinics and UMKC School of Medicine, Kansas City, MO	ASCPT President's Award	
Louisville	Amanda Myers, MD, MSPH	2004 - 2006	PPRU Adjunct Clinical Pharmacologist	Assistant Professor of Pediatrics, Division of Emergency Medicine; Medical staff of the Kosair Charities Pediatric Clinical Research Unit and Louisville PPRU. Louisville, KY		
Louisville	Carmen T. Condurache, M.D.	2007 -	PPRU Adjunct Clinical Pharmacologist	Instructor in Pediatrics, Division of Hospitalists and Kosair Charities Pediatric Clinical Research Unit and Louisville PPRU. Louisville, KY		
Louisville	Katherine Potter, M.D.	2004 - 2007	Fellow	Assistant Professor, Division of Pediatric Critical Care, Department of Pediatrics, University of Louisville, Louisville, KY		
LSU	Kim Adcock, MD	1998-2000	Fellow	Assistant Professor Pediatrics/University of Mississippi Medical Center		
LSU	Roy Parish, PharmD	1995-1996	Fellow	British Health Service		
LSU	Margaret Ann Springer, MD	2001-2003	Faculty trainee	Assistant Professor Pediatrics/LSUHSC-Shreveport		
LSU	Renee Simar, PhD	1995	Staff trainee	Industry		
LSU	James Hinson, MD	1996	Graduate student	Industry		
LSU	Tonya Slusher, MD	1999-2000	Fellow	Private Practice/Green Clinic Ruston, LA		
Tennessee	Shannan Eades, Pharm.D.	7/1/96 - 6/30/98	Pediatric Clinical Pharmacology	Director Clinical Pharmacy Services, National Children's Hospital, Washington, DC		
Tennessee	Robin Mottern, Pharm.D.	7/1/99-6/30/00	Pediatric Clinical Pharmacology	Pediatric Clinical Pharmacist, Denver Children's Hospital		
Tennessee	Majed Al-Jeraisy, Pharm.D.	7/1/00-6/30/01	Pediatric Clinical Pharmacology	Director Pediatric Clinical Pharmacy Services, King Faisal Hospital, Riyadh, Saudi Arabia		
Tennessee	John Whitworth, M.D.	7/1/06-6/30/03	Pediatric Clinical Trials	Fellow, Pediatric Gastroenterology, University of Colorado College of Medicine, Denver Children's Hospital		
UCSD	Linda Wu, Pharm.D.	7/1994-6/1995	Fellowship	Clinical Faculty Appointment with Univeristy of Toledo School of Pharmacy		
UCSD	Mark Mirochnick, MD	9/1997-3/1998	Mini-sabatical	Professor & Chief Neonatology, Boston University Medical Center		
UCSD	Brookie Best, Pharm.D.	7/2000-6/2004	Fellowship / NRSA	UCSD PPRU-Associate Pharmacologist; Faculty UCSD School of Pharmacy and Pediatrics		
UCSD	Suzette Blanchard, Ph.D.	5/2002-4/2005	K25 (EC mentor)	Faculty at City of Hope Hospital		
UCSD	Parul Patel, Pharm.D.	6/2004-9/2005	Fellowship	GSK Research Scientist		
UCSD	Adrina Herrera-Tremolet, M.D.	7/2006-6/2007	Fellowship	Faculty UCSD School of Medicine, K23 awardee		
UCSD	Elizabeth Sarles, Pharm.D.	2006-2007		Pharmacy student		
Utah	W. Ellaria Lee, PharmD	7/1/2000-6/30/2002	Pediatric Clinical Pharmacology	CHOP		
Utah	Kristin Satterfield, PhD	7/1/2005-7/1/2007	Pediatric Clinical Pharmacology fellowship	Medical Student University of Utah		
Utah	Christopher Ortaon, PhD	8/1/2006-present	Postdoctoral fellowship in Pediatric Clinical Pharmacology studying pulmonary metabolism of steroids by CYPs 3A4,5,7	Fellow, University of Utah		
UTSW	Roberto Santos, MD	2005-2008		UTSW		
Wayne	Randy Prescilla, MD	1999-2001	Clinical Pharmacology Fellowship	Assistant Professor of Pediatrics Children's Hospital, Harvard, Boston		
Wayne	Hakan Ergun, MD, PhD	2000-2002	Clinical Pharmacology Fellowship	Professor of Pharmacology University of Ankara Turkey		
Wayne	Daniel Frattarelli, MD	2001-2003	Clinical Pharmacology Fellowship	Attending Pediatrician - Henry Ford Medical Center, Asst Professor of Pediatrics-Wayne State Univ, Detroit		
Wayne	Indu Warrier, MD	2003-2006	Pediatric Clinical Pharmacology Fellowship including 1 year of Allergy-Immunology-Pharmacology	Fellow, Wayne St		
Wayne	Merene Mathew, MD	(Completing 12-2006) 2006-2008	Clinical and Molecular Pharmacology Fellowship	Fellow, Wayne St		

Appendix J

List of Publications with Multi Disciplinary Investigators

Examples of PPRU Multidisciplinary Studies (2001-2004)

James LP, Simpson PM, Farrar HC, **Kearns GL**, Wasserman GS, **Blumer J**, **Reed MD**, **Sullivan JE**, Hinson JA, and the **PPRU Network**. Cytokines and toxicity in acetaminophen overdose. *Journal of Clinical Pharmacology*. October 2005; 45: 1165-1171. (**Emergency Departments, Hospitalist services and PICUs of multiple sites**)

Kovacs A, Montepiedra G, Carey V, Pahwa S, Weinberg A, Frenkel L, **Capparelli E**, Mofenson L, Smith E, McIntosh K, Burchett SK. Immune Reconstitution following HAART in Children with Advanced or Progressive HIV Disease and Complete or Partial Viral Load Response. *Journal of Infectious Diseases*. 2005; 192: 296-302 (**Collaboration with HIV programs in multiple institutions**)

Daw NC, Furman WL, Stewart CF, Iacono LC, Krailo M, Bernstein ML, Dancey JE, Speights RA, **Blaney SM**, Reaman GH, **Adamson PA**. A phase I and pharmacokinetic study of gefitinib in children with refractory solid tumors: **A Children's Oncology Group study**. *Journal of Clinical Oncology*. 2005; 23: 6172-6180.

Kovacs A, Cowles MK, Britto P, **Capparelli E**, Fowler MG, Jeremy RJ, Moye J, McIntosh K, Rathore MH, Pitt J, Husson RN. Pharmacokinetics of Didanosine and Drug Resistance Mutations in Infants Exposed to ZDV during Gestation or Postnatally and Treated with Didanosine or Zidovudine in the First Three Months of Life. *Pediatric Infectious Disease Journal*. 2005; 24: 503-509 (**Collaborations with HIV and Obstetrical programs**).

Acosta EP, Brundage RC, King JR, **Sanchez PJ**, Sood S, Agrawal V, Homans J, **Jacobs RF**, Lang D, Romero JR, Griffin J, Cloud G, Whitley R, Kimberlin DW. Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid valganciclovir formulation. *Clinical Pharmacology and Therapeutics*, 2007 Jun; 81(6):867-72. (**Neonatal units in multiple centers**)

Benjamin DK, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins R, Duara S, Poole K, Laptook A, Goldberg R. Neonatal Candidiasis Among Extremely Low Birth Weight Infants: Risk Factors Mortality, and Neurodevelopmental Outcomes at 18-22 Months. *Pediatrics*. 2006 Jan;117(1):84-92. (**Neonatal Fungal Study Group**)

Gururangan S, Petros WP, Poussaint TY, Hancock ML, Phillips PC, Friedman HS, **Bomgaars L**, **Blaney SM**, Kun LE, Boyett JM. Phase I trial of intrathecal spartaject busulfan in children with neoplastic meningitis: **a Pediatric Brain Tumor Consortium Study** (PBTC-004). *Clinical Cancer Research*. March 2006; 12(5): 1540-1546

Susan M Abdel-Rahman, Pharm.D.; David P Benziger, Ph.D.; **Richard F Jacobs**, M.D.; **Hasan S Jafri**, M.D.; Erica Fischer Hong, MPH; **Gregory L. Kearns**, Pharm.D., Ph.D. Single-dose pharmacokinetics of daptomycin in children with suspected or proved Gram-positive infections. *Pediatr Infect Dis J* 2008 (April). (**Infectious Disease services of multiple sites**)

Blake MJ, Abdel-Rahman SM, Jacobs RF, Lowery NK, Sterling TR, **Kearns GL**. Pharmacokinetics of rifapentine in children. *Pediatr Infect Dis J*. 2006; 25(5):405-9. (**Collaboration with CDC Tuberculosis programs**)

Daniel K. Benjamin, Jr, Barbara J. Stoll, **Avory A. Fanaroff**, Scott A. McDonald, William Oh, Rosemary D. Higgins, Shahnaz Duara, Kenneth Poole, **Abbot Laptook**, Ronald Goldberg and on behalf of the National Institute of Child Health and Human Development Neonatal Research Network. Neonatal Candidiasis Among Extremely Low Birth Weight Infants: Risk Factors, Mortality Rates, and Neurodevelopmental Outcomes at 18 to 22 Months *Pediatrics* 2006; 117: 84-92 (**Collaboration of PPRU and the Neonatal Research Network, NICHD**)

Daniel K. Benjamin, Jr, MD, MPH, PhD, Elizabeth R. DeLong, PhD, William J. Steinbach, MD, Charles M. Cotton, MD, Thomas J. Walsh, MD, and Reese H. Clark, MD Empirical Therapy for Neonatal Candidemia in Very Low Birth Weight Infants. *Pediatrics* 2003; 112:543-7 (**PPRU and Pediatrix Medical Group**)

Thompson P, Gupta M, Rosner G, Yu A, **Barrett J, Bomgaars L**, Bernstein M, **Blaney S**, Mondick J. Pharmacokinetics of irinotecan and its metabolites in pediatric cancer patients: A report from the children's oncology group. *Cancer Chemotherapy and Pharmacology* 2008 (**MSCIDA project of PPRU site in cooperation with COG**)

Jiang Z, Dragin N, **Jorge-Nebert LF**, Martin MV, Guengerich FP, Aklillu E, et al. Search for an association between the human CYP1A2 genotype and CYP1A2 metabolic phenotype. *Pharmacogenet Genomics* 2006; 16(5):359-67 (**Multi disciplinary pharmacogenetics group spearheaded by Dan Nebert**)

Weimert NA, DeRotte M, Alloway RR, Woodle ES and **Vinks AA**. Monitoring of Inosine Monophosphate Dehydrogenase Activity as a Biomarker for Mycophenolic Acid Effect: Potential Clinical Implications. *Ther Drug Monit*, 2007 29(2): 141-149 (**Collaboration between kidney transplant programs at UC and CCHMC**)
This has now expanded to 3 other PPRU sites: Utah, Arkansas and Dallas

Examples of studies of the PPRU in collaboration with other networks (Past and Future)

J. Steven Leeder, PharmD, PhD; Bob Batterson, MD ADR: Atypical Antipsychotic-Induced Weight Gain/Obesity. **Proposed study of PPRU and the NIGMS-supported Pharmacogenetics Research Network (PGRN).**

Susan Rahman Disruptions in bilirubin translocation related to developmental, genetic and environmental factors that alter the expression and/or activity of OATP transporters. **Proposed collaboration with the PPRU and an OPRU center in Galveston, TX**

Laura Greer (Fellow in OB/GYN), **Jeanne Sheffield, Pablo Sanchez and George McCracken** Clinical pharmacology of oseltamivir in pregnant and post-partum women. **Collaboration with PPRU and OPRU** (Protocol to be submitted to PPRU and OPRU soon)

Sanchez, Pablo David Kimberlin and other centers in PPRU and CASG. Pharmacokinetics and safety of oseltamivir in infants and young children **Collaboration of PPRU centers and the Collaborative Antiviral Study Group [CASG]**, currently in progress

Sanchez, P Ward, R and investigators from Neonatal Research network. Study of inositol in newborn infants. **Collaboration of PPRU and Neonatal Research Network centers.** In progress

Ardura, Monica (Fellow), **Ramilo, O, Kaplan, S** and others. Clinical Benefit of Adding a Bactericidal Antibiotic and Application of Transcriptional Profiles in Pediatric Patients with *Staphylococcus aureus* Sepsis. **Proposed study of PPRU centers and the NIGMS-supported Pharmacogenetics Research Network (PGRN).**

Aman MG, **Vinks AA**, Remmerie, B, Mannaert E, Ramadan Y, Masty, J, Lindsay RL, Malone K,. Plasma pharmacokinetics of risperidone and their relationship to saliva concentrations in children with psychiatric or neurodevelopmental disorders. *Clinical Therapeutics*, 2007, 29 (7): 1476-1486 **Collaboration with the Research Units of Pediatric Psychopharmacology (RUPP) network**

Benjamim, D et al Fluconazole prophylaxis for prevention of neonatal candidiasis. **Collaboration between PPRO and Pediatrix centers**, one of several on-going studies

Azbug MJ, Cloud G, Bradley J, **Sanchez P**, Romero J, Powell D, Lepow M, Mani C, **Capparelli EV**, Blount S, Lakeman F, Whitley RJ, Kimberlin DW. Double-blind, placebo-controlled trial of pleconaril in infants with enterovirus meningitis. *Ped Infect Dis J* 2003; 22:335-41. **A collaborative effort with the CASG**

Capparelli EV, van den Anker J, Brown K, Baren J, Mahajan P, Vance C, Lillis K, Stanley R, Davis D, Singh T, **Blumer J**, Chamberlain J, and the PPRU and PECARN Networks. Lorazepam pharmacokinetics in Children with status epilepticus. (Abstract) PAS-SPR 2007, Toronto CA. **Collaboration with PECARN**

Mirochnick M, Thomas T, **Capparelli E**, Zeh C, Holland D, Masaba R, Odhiambo P, Fowler MG, Weidle PJ, Thigpen M. Plasma antiretroviral concentrations in breast-feeding infants whose mothers are receiving HAART. Presented at Conference for Retroviruses and Opportunistic Infections 2007 Study in a neonatal population in **collaboration with CDC support KISUMU** (PPRU approved support for assay development)