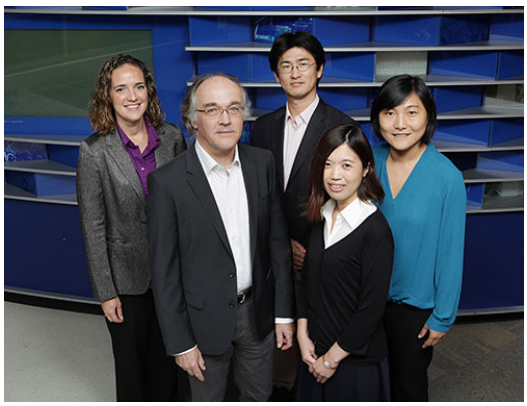
Clinical Pharmacology

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	4
Joint Appointment Faculty	3
Research Fellows and Post Docs	7
Research Graduate Students	1
Total Annual Grant Award Dollars	$77,445
Total Annual Industry Award Dollars	$282,532
Total Publications	27

CLINICAL ACTIVITIES AND TRAINING	
Clinical Fellows	1



Row 1: S Vinks, C Emoto

Row 2: L Ramsey, T Fukuda, M Dong

Research Highlights

Alexander (Sander) A. Vinks, PharmD, PhD, FCP

Implementation of Model-based Precision Dosing

Alexander (Sander) A. Vinks, PharmD, PhD, FCP, is developing systems for precision dosing of several different medications to allow the tailoring of dose to individual needs in real time. With the support of an Innovation Fund Award, he and his team have developed an innovative prototype systems pharmacology platform for individualized morphine treatment in neonates. The study involved a multidisciplinary team including Joshua Euteneuer, MD, a neonatology fellow who participates in the T32 Pediatric Clinical Pharmacology Training Program. The study, conducted in parallel with the Perinatal Institute's Pilot and Feasibility Program grant, developed a rapid bedside test for the measurement of morphine in blood led by Dr. Vinks. This cloud-based technology will help clinicians decide how much morphine to give to newborn babies. The platform, which integrates with the electronic health record, uses genetic markers, demographic data, clinical data and lab results to suggest individualized dosing.

Chie Emoto, PhD

Physiologically-based pharmacokinetic (PBPK) models for precision dosing in neonates

Chie Emoto, PhD, developed an innovative physiologically-based pharmacokinetic (PBPK) model of morphine for neonates and small infants using data obtained from ongoing clinical studies in pediatric patients after tonsillectomy (PI: Senthilkumar Sadhasivam, MD). This predictive computer model helps physicians fine-tune doses to maintain target morphine concentrations in neonates based on patients' physiological parameters. This study was accepted for publication in *CPT Pharmacometrics Systems Pharmacology*, which is an official journal of the *American Society of Clinical Pharmacology and Therapeutics*.

Tsuyoshi Fukuda, PhD

Eculizumab treatment optimization for children with severe thrombotic microangiopathy

Tsuyoshi Fukuda, PhD, in collaboration with members of the Division of Bone Marrow Transplantation and Immune Deficiency led a population pharmacokinetics and pharmacodynamics analysis of eculizumab in patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). The developed PK/PD model will form the basis for an Eculizumab (Soliris) individualized dosing strategy for children with severe thrombotic microangiopathy. The first results were published in the journal *Biology of Blood and Marrow Transplantation* the official journal of the *American Society for Blood and Marrow Transplantation*.

During the 2016 Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics, one of our research fellows, for whom Drs. Fukuda and Vinks, serve as mentors, received the President's Trainee Award for this work.

Renewal of NIH Program to Train the Next generation of Pediatric Clinical Pharmacologist

This year our pediatric clinical pharmacology training program was successful in the competitive renewal process. We are now one of five sites in the U.S. awarded a pediatric clinical and developmental pharmacology training grant from the National Institute of Child Health and Development (NICHD). This postdoctoral program trains clinical investigators to assume leadership roles in evaluating pediatric therapeutics. Many medicines have not been studied for use in children, and few medicines developed are specifically made to treat childhood diseases. One of our major goals is to support and train fellows in applying pharmacokinetics and pharmacogenetics/genomics to individualized therapy. Our program actively participates in the Adult and Pediatric Clinical Pharmacology Training Network established by the National Institutes of General Medical Sciences (NIGMS) and Child Health and Development as a strategic initiative to increase the pool of pediatric clinical pharmacologists.

Pharmacometrics Program Revolutionizing How We Perform Drug Studies in Children

Our Pharmacometrics Services Program continues to provide unique pediatric expertise to improve pediatric drug development and enhance the success rate of drug studies in neonates, infants, children and adolescents. The program provides modeling and simulation consultation for internal programs and external costumers. Last year's multiple clinical trials included studies evaluating sirolimus in the treatment of vascular anomalies, everolimus in patients with tuberous sclerosis, hydroxyurea individualized dosing in children with sickle cell anemia, and precision dosing of biologics such as infliximab (Remicade) in Crohn's disease, and eculizumab (Soliris) and alemtuzumab (Campath) in patients undergoing hematopoietic stem cell transplantation. Our research explores the developmental characteristics and genetic polymorphisms of drug metabolizing enzymes and receptors. Among these projects, Chie Emoto, PhD, leads a study that focuses on developing physiologically-based pharmacokinetic models for morphine, methadone and mTOR inhibitors such as sirolimus.

Significant Publications

Wiles JR, Isemann B, **Mizuno T**, Tabangin ME, Ward LP, Akinbi H, **Vinks AA. Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome: A Pilot Study**. *J Pediatr*. 2015 Dec;167(6):1214-20 e3.

This study characterized the population pharmacokinetic (PK) of oral methadone in neonates requiring pharmacologic treatment of neonatal abstinence syndrome (NAS) and developed a PK model towards an evidence-based treatment protocol. Researchers assessed concentrations of methadone and its metabolites via high performance liquid chromatography-tandem mass spectrometry from dried blood spots. They performed population PK analysis to determine the volume of distribution and clearance of oral methadone. Researchers simulated methadone plasma concentration-time profiles from the deduced PK model to optimize the dosing regimen. The study developed a new dosing and expedited weaning protocol for patients requiring pharmacologic treatment of NAS. The proposed dosing regimen may reduce the cumulative dose of opioid and shorten the length of hospitalization and is currently being prospectively evaluated.

Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, Wang D, **Vinks AA**, He Y, Swen JJ. **Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing**. *Clin Pharmacol Ther*. 2015 Jul;98(1):19-24.

Tacrolimus is the mainstay immunosuppressant drug used after solid organ and hematopoietic stem cell transplantation. Individuals who express CYP3A5 (extensive and intermediate metabolizers) generally have decreased dose-adjusted trough concentrations of tacrolimus as compared with those who are CYP3A5 non-expressers (poor metabolizers), possibly delaying achievement of target blood concentrations. In this study, we summarized evidence from the published literature supporting this association and provide dosing recommendations for tacrolimus based on CYP3A5 genotype when known (updates at www.pharmgkb.org).

Jodele S, **Fukuda T**, **Mizuno K**, **Vinks AA**, Laskin BL, Goebel J, Dixon BP, Chima RS, Hirsch R, Teusink A, Lazear D, Lane A, Myers KC, Dandoy CE, Davies SM. **Variable Eculizumab Clearance Requires Pharmacodynamic Monitoring to Optimize Therapy for Thrombotic Microangiopathy after Hematopoietic Stem Cell Transplantation**. *Biol Blood Marrow Transplant*. 2016 Feb;22(2):307-15.

Thrombotic microangiopathy (TMA) after hematopoietic stem cell transplant (HSCT) associated with terminal complement activation, as measured by elevated plasma terminal complement (sC5b-9) concentrations, has a very high mortality. The complement inhibitor eculizumab may be a therapeutic option for HSCT-associated TMA. We examined the pharmacokinetics and pharmacodynamics (PK/PD) of eculizumab in children and young adult HSCT recipients with TMA and activated complement to determine drug dosing requirements for future efficacy trials. Sixty one percent of treated patients had complete resolution of TMA, and were able to safely discontinue eculizumab without disease recurrence. Overall survival was significantly higher in treated subjects compared to untreated patients (56% versus 9%, p=0.003). Population PK/PD analyses correlated eculizumab concentrations with complement blockade and clinical response and determined inter-individual differences in PK parameters. Our eculizumab dosing algorithm accurately determined eculizumab concentration-time profiles for HSCT recipients with high-risk TMA. This algorithm may guide eculizumab treatment and ensure that future efficacy studies use the most clinically appropriate and cost-efficient dosing schedules.

Emoto C, **Fukuda T**, **Venkatasubramanian R**, **Vinks AA**. **The impact of CYP3A5*3 polymorphism on sirolimus pharmacokinetics: insights from predictions with a physiologically-based pharmacokinetic model**. *Br J Clin Pharmacol*. 2015 Dec;80(6):1438-46.

Sirolimus is an mTOR inhibitor metabolized by CYP3A4 and CYP3A5. Reported effects of CYP3A5 polymorphisms on sirolimus pharmacokinetics (PK) have shown unexplained discrepancies across studies. We quantitatively assessed the effect of CYP3A5*3 status on sirolimus PK by in vitro assessment and simulation using a physiologically-based PK (PBPK) model. In addition, we explored designs for an adequately powered pharmacogenetic association study. The PBPK model predicted a small CYP3A5*3 effect on simulated sirolimus PK profiles. A subsequent power analysis based on these findings indicated that at least 80 subjects in an enrichment design, 40 CYP3A5 expressers and 40 non-expressers, is required to detect a significant difference in the predicted trough concentrations at 1 month of therapy ($P < 0.05$, 80% power). This study suggests that CYP3A5 contribution to sirolimus metabolism is much smaller than that of CYP3A4. The result of inadequate sample size could explain observed discrepancies across published studies. PBPK model simulations allowed mechanism-based evaluation of the effects of CYP3A5 genotype on sirolimus PK and provide preliminary data for the design of an adequately powered prospective study.

Dong M, McGann PT, **Mizuno T**, Ware RE, **Vinks AA. Development of a pharmacokinetic-guided dose individualization strategy for hydroxyurea treatment in children with sickle cell anaemia**. *Br J Clin Pharmacol*. 2016 Apr;81(4):742-52.

Hydroxyurea has emerged as the primary disease-modifying therapy for patients with sickle cell anaemia (SCA). The laboratory and clinical benefits of hydroxyurea are optimal at maximum tolerated dose (MTD), but the current empirical dose escalation process often takes up to 12 months. The purpose of this study was to develop a pharmacokinetic-guided dosing strategy to reduce the time required to reach hydroxyurea MTD in children with SCA. Researchers analyzed pharmacokinetic (PK) data from the HUSTLE trial (NCT00305175) by using non-linear mixed effects modeling (Nonmem 7.2). The study evaluated A D-optimal sampling strategy to estimate individual PK and hydroxyurea exposure (area under the concentration-time curve (AUC)). We developed a PK model-based individualized dosing strategy for the prospective Therapeutic Response Evaluation and Adherence Trial (TREAT, ClinicalTrials.gov NCT02286154). This approach has the potential to optimize the dose titration of hydroxyurea therapy for children with SCA, to achieve clinical benefits at MTD more quickly.

Division Publications

1. Adams DM, Trenor CC, 3rd, Hammill AM, Vinks AA, Patel MN, Chaudry G, Wentzel MS, Mobberley-Schuman PS, Campbell LM, Brookbank C, Gupta A, Chute C, Eile J, McKenna J, Merrow AC, Fei L, Hornung L, Seid M, Dasgupta AR, Dickie BH, et al. **Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies.** *Pediatrics*. 2016; 137:e20153257.

2. Arya R, Gillespie CW, Cnaan A, Devarajan M, Clark P, Shinnar S, Vinks AA, Mizuno K, Glauser TA, Childhood Absence Epilepsy Study G. **Obesity and Overweight as Cae Comorbidities and Differential Drug Response Modifiers.** *Neurology*. 2016; 86:1613-21.

3. Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, Wang D, Vinks AA, He Y, Swen JJ, Leeder JS, van Schaik R, Thummel KE, Klein TE, Caudle KE, MacPhee IA. **Clinical Pharmacogenetics Implementation Consortium (Cpic) Guidelines for Cyp3a5 Genotype and Tacrolimus Dosing.** *Clin Pharmacol Ther*. 2015; 98:19-24.

4. Brouwer KL, Aleksunes LM, Brandys B, Giacoia GP, Knipp G, Lukacova V, Meibohm B, Nigam SK, Rieder M, de Wildt SN, Pediatric Transporter Working Group. **Human Ontogeny of Drug Transporters: Review and Recommendations of the Pediatric Transporter Working Group.** *Clin Pharmacol Ther*. 2015; 98:266-87.

5. Chidambaran V, Venkatasubramanian R, Sadhasivam S, Esslinger H, Cox S, Diepstraten J, Fukuda T, Inge T, Knibbe CA, Vinks AA. **Population Pharmacokinetic-Pharmacodynamic Modeling and Dosing Simulation of Propofol Maintenance Anesthesia in Severely Obese Adolescents.** *Paediatr Anaesth*. 2015; 25:911-23.

6. Chidambaran V, Venkatasubramanian R, Zhang X, Martin LJ, Niu J, Mizuno T, Fukuda T, Meller J, Vinks AA, Sadhasivam S. **Abcc3 Genetic Variants Are Associated with Postoperative Morphine-Induced Respiratory Depression and Morphine Pharmacokinetics in Children.** *Pharmacogenomics J*. 2016.

7. Christians U, Vinks AA, Langman LJ, Clarke W, Wallemacq P, van Gelder T, Renjen V, Marquet P, Meyer EJ. **Impact of Laboratory Practices on Interlaboratory Variability in Therapeutic Drug Monitoring of Immunosuppressive Drugs.** *Ther Drug Monit*. 2015; 37:718-24.

8. Dong M, McGann PT, Mizuno T, Ware RE, Vinks AA. **Development of a Pharmacokinetic-Guided Dose Individualization Strategy for Hydroxyurea Treatment in Children with Sickle Cell Anaemia.** *Br J Clin Pharmacol*. 2016; 81:742-52.

9. Downes K, Goldstein S, Vinks A. **Increased Vancomycin Exposure and Nephrotoxicity in Children: Therapeutic Does Not Mean Safe.** *J Pediatr Infect Dis Soc*. 2016; 5:65-67.

10. Emoto C, Fukuda T, Venkatasubramanian R, Vinks AA. **The Impact of Cyp3a5*3 Polymorphism on Sirolimus Pharmacokinetics: Insights from Predictions with a Physiologically-Based Pharmacokinetic Model.** *Br J Clin Pharmacol*. 2015; 80:1438-46.

11. Emoto C, Vinks AA, Fukuda T. **Risk Assessment of Drug-Drug Interactions of Calcineurin Inhibitors Affecting Sirolimus Pharmacokinetics in Renal Transplant Patients.** *Ther Drug Monit*. 2016; 38:607-13.

12. Gist KM, Goldstein SL, Joy MS, Vinks AA. **Milrinone Dosing Issues in Critically Ill Children with Kidney Injury: A Review.** *J Cardiovasc Pharmacol*. 2016; 67:175-81.

13. Gist KM, Mizuno T, Goldstein SL, Vinks A. **Retrospective Evaluation of Milrinone Pharmacokinetics in Children with Kidney Injury.** *Ther Drug Monit*. 2015; 37:792-6.

14. Hahn A, Frenck RW, Jr., Allen-Staat M, Zou Y, Vinks AA. **Evaluation of Target Attainment of Vancomycin Area under the Curve in Children with Methicillin-Resistant Staphylococcus Aureus Bacteremia.** *Ther Drug Monit*. 2015; 37:619-25.

15. Hahn A, Fukuda T, Hahn D, Mizuno T, Frenck RW, Jr., Vinks AA. **Pharmacokinetics and Pharmacogenomics of Beta-Lactam-Induced Neutropenia.** *Pharmacogenomics*. 2016; 17:547-59.

16. Hayashi S, Ohashi K, Mihara S, Nakata E, Emoto C, Ohta A. **Discovery of Small-Molecule Nonpeptide Antagonists of Nociceptin/Orphanin Fq Receptor: The Studies of Design, Synthesis, and Structure-Activity Relationships for (4-Arylpiperidine Substituted-Methyl)-[Bicyclic (Hetero)Cycloalkanobenzene] Derivatives.** *Eur J Med Chem*. 2016; 114:345-64.

17. Jodele S, Fukuda T, Mizuno K, Vinks AA, Laskin BL, Goebel J, Dixon BP, Chima RS, Hirsch R, Teusink A, Lazear D, Lane A, Myers KC, Dandoy CE, Davies SM. **Variable Eculizumab Clearance Requires Pharmacodynamic Monitoring to Optimize Therapy for Thrombotic Microangiopathy after Hematopoietic Stem Cell Transplantation.** *Biol Blood Marrow Transplant*. 2016; 22:307-15.

18. Nehus EJ, Mizuno T, Cox S, Goldstein SL, Vinks AA. **Pharmacokinetics of Meropenem in Children Receiving Continuous Renal Replacement Therapy: Validation of Clinical Trial Simulations.** *J Clin Pharmacol*. 2016; 56:291-7.

19. Ngamprasertwong P, Dong M, Niu J, Venkatasubramanian R, Vinks AA, Sadhasivam S. **Propofol Pharmacokinetics and Estimation of Fetal Propofol Exposure During Mid-Gestational Fetal Surgery: A Maternal-Fetal Sheep Model.** *PLoS One*. 2016; 11:e0146563.

20. Rohan JM, Fukuda T, Alderfer MA, Wetherington Donewar C, Ewing L, Katz ER, Muriel AC, Vinks AA, Drotar D. **Measuring Medication Adherence in Pediatric Cancer: An Approach to Validation.** *J Pediatr Psychol*. 2016.

21. Rosen MJ, Minar P, Vinks AA. **Letter: Stool Adalimumab Detection in Ulcerative Colitis and Crohn's Disease--Authors' Reply.** *Aliment Pharmacol Ther*. 2015; 42:241.

22. Shokati T, Bodenberger N, Gadpaille H, Schniedewind B, Vinks A, Jiang W, Alloway R, Christians U. **Quantification of the Immunosuppressant Tacrolimus on Dried Blood Spots Using Lc-Ms/Ms.** *J Vis Exp*. 2015; 8:e52424.

23. Teusink A, Vinks A, Zhang K, Davies S, Fukuda T, Lane A, Nortman S, Kissell D, Dell S, Filipovich A, Mehta P. **Genotype-Directed Dosing Leads to Optimized Voriconazole Levels in Pediatric Patients Receiving Hematopoietic Stem Cell Transplantation.** *Biol Blood Marrow Transplant*. 2016; 22:482-6.

24. Vinks A. **Therapeutic Optimization as Part of the Precision Medicine Paradigm.** *Clin Pharmacol Ther*. 2016; 99:340-42.

25. Vinks AA, Emoto C, Fukuda T. **Modeling and Simulation in Pediatric Drug Therapy: Application of Pharmacometrics to Define the Right Dose for Children.** *Clin Pharmacol Ther*. 2015; 98:298-308.

26. Wiles JR, Isemann B, Mizuno T, Tabangin ME, Ward LP, Akinbi H, Vinks AA. **Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome: A Pilot Study.** *J Pediatr*. 2015; 167:1214-20 e3.

27. Yang X, Sherwin CM, Yu T, Yellepeddi VK, Brunner HI, Vinks AA. **Pharmacokinetic Modeling of Therapies for Systemic Lupus Erythematosus.** *Expert Rev Clin Pharmacol*. 2015; 8:587-603.

Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Alexander Vinks, PHD	Pharmacokinetic Studies of Tacrolimus in Transplant Patients	Food and Drug Administration (University of Cincinnati)	U01 FD004573	9/15/2012 - 9/14/2016	$77,445
Total Annual Grant Award Dollars					**$77,445**

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Alexander Vinks, PHD	Pharmacometrics	$282,532
Total Annual Industry Award Dollars		**$282,532**