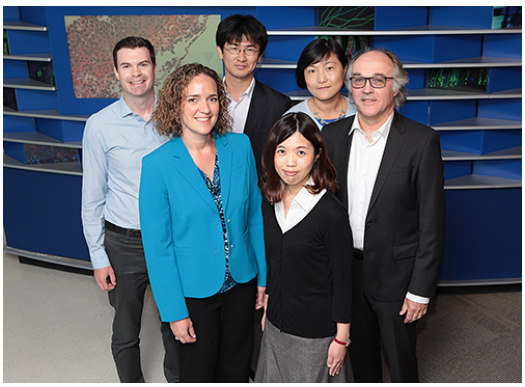
Clinical Pharmacology

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	4
Joint Appointment Faculty	3
Research Fellows and Post Docs	8
Research Graduate Students	1
Total Annual Grant Award Dollars	$336,471

CLINICAL ACTIVITIES AND TRAINING	
Staff Psychiatrists	1
Clinical Fellows	2



Row 1: L Ramsey, C Emoto, S Vinks

Row 2: T Phoenix, T Fukuda, M Dong

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Division Highlights

Alexander "Sander" A. Vinks, PharmD, PhD, FCP

Dr. Alexander (Sander) Vinks, PharmD, PhD, FCP, received the senior faculty Mentoring Achievement Award for his commitment to the training of the next generation of pediatric clinical pharmacology scientists. In addition, the National Institute of Mental Health (NIMH) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) selected his T32 clinical pharmacology training program to become the first pilot site to provide fellowship training for the next generation of pediatric clinical psychopharmacology physician-scientists.

Tsuyoshi Fukuda, PhD

Dr. Tsuyoshi Fukuda, PhD, in collaboration with members of the Division of Bone Marrow Transplantation and Immune Deficiency Research led pharmacokinetic and pharmacodynamic (PK/PD) modeling studies of alkylating agents (melphalan and busulfan) and therapeutic antibodies (Alemtuzumab) in patients undergoing hematopoietic stem cell transplantation. The predictive PK/PD models help physicians implement individualized precision dosing strategies for their patients. The presentation of the results of these successful efforts occurred at the annual meetings of the American Society of Blood and Marrow Transplantation, the American Society of Hematology, and the American Society for Clinical Pharmacology and Therapeutics.

Chie Emoto, PhD

Physiologically-based pharmacokinetic (PBPK) model of morphine and developmental change in transporter expression in neonates

Dr. Chie Emoto, PhD, developed an innovative physiologically-based pharmacokinetic (PBPK) model of morphine using data from children after tonsillectomy obtained in collaborative clinical studies with colleagues in the Department of Anesthesiology. This predictive computer model helps physicians anticipate morphine pharmacokinetic differences based on patient demographics and physiology. Using pediatric liver samples obtained from the Better Outcomes for Children Biorepository, the model was further enriched with data on developmental

changes in hepatic Organic Cation Transporter expression, which controls hepatic uptake and is an important predictor of morphine metabolism in neonates and small infants. These studies received acceptance for publication in *CPT Pharmacometrics Systems Pharmacology* and *Drug Metabolism and Disposition*, the official journals of the American Society of Clinical Pharmacology and Therapeutics, and the American Society for Pharmacology and Experimental Therapeutics, respectively.

One of our research fellows, for whom Drs. Emoto and Fukuda serve as mentors, received the President's Trainee Award for this work at the 2017 Annual Meeting of the American Society of Clinical Pharmacology and Experimental Therapeutics in Washington, DC.

Min Dong, PhD

Dr. Min Dong, PhD, has been a team leader in the Pharmacometrics Center of Excellence Program providing high level pharmacometrics expertise for pediatric study design optimization, clinical trial simulations, dose selection approaches, and protocol development for pharmacokinetic (PK) and pharmacodynamic (PD) studies. She recently led the effort of developing an optimal trial design for a clinical study of loxapine for inhalation in children. The study design formed the basis for a Phase I clinical trial and represents a proof of concept of the application of modeling and simulation in support of study design in pediatric studies. The approach has great merit as being less invasive and generalizable for the design and analysis of other drug studies in children. The journal of *Clinical Pharmacokinetics* will publish the results. Dr. Dong is also continuing her efforts on the model-informed precision dosing studies of hydroxyurea in children with sickle cell anemia in collaboration with the Division of Hematology.

NIH T32 Pediatric Clinical Pharmacology Postdoctoral Training Program

Our fellowship in clinical pharmacology progam is one of only five sites in the US with an active program supported by the National Institute of Child Health and Development (NICHD). This year the National Institute of Mental Health (NIMH) and NICHD have selected our T32 clinical pharmacology program to be the first training program to pilot the training of the next generation of clinical researchers in pediatric clinical psychopharmacology. NIMH has identified a critical gap in their research portfolio in early stage pediatric clinical trial design, and we are the first program awarded this important training position. The goal of the postdoctoral program is to train clinical investigators to assume leadership roles in improving pediatric therapeutics. Many medicines are not studied for use in newborns and children, and few medicines are specifically developed to treat childhood diseases. Our program supports, and trains, fellows in applying pharmacokinetics and pharmacogenetics/genomics as part of study design as well as precision medicine approaches. We actively participate in the Adult and Pediatric Clinical Pharmacology Training Network established by NICHD, and the National Institutes of General Medical Sciences (NIGMS), as a strategic initiative to increase the pool of well-trained pediatric clinical pharmacologists.

Pharmacometrics Center of Exellence

Our program has experienced considerable growth with our service offerings, increased project diversity, and client base, including in-house, biopharmaceutical, biotechnology, and specialty pharmaceutical companies seeking expertise to determine optimal clinical trial design and pharmacometrics analysis as part of drug studies in neonates and children. Our program offers strategic clinical pharmacology consulting and pharmacometric services to help clients improve drug development and regulatory decision-making throughout the clinical development process to increase the success rate of pediatric and adult drug studies. Our team has demonstrated expertise in clinical pharmacology, providing PK/PD support and data analysis, model-based drug development strategies, PK/PD modeling & simulation, study design optimization, clinical trial simulation, and the development of model-informed precision dosing strategies.

NeoRelief: a Decision Support Platform to Revolutionize How We Perform Precision Dosing in Neonates

At the end of the fiscal year, we launched NeoRelief–a pharmacokinetics model-informed electronic health record (EHR) embedded decision support platform that will enable precision dosing of morphine in the management of neonatal pain. The platform builds on ongoing research conducted over the past three years supported by the CCTST, internal Pilot & Feasibility Program, and Innovation Funding sources. As part of the NeoRelief platform a rapid turnaround paper spray assay for morphine and metabolites using a single drop of blood developed by colleagues in the Clinical Mass Spectrometry Laboratory. The combination of dry blood spot technology with predictive systems pharmacology models will allow real-time forecasting and precision dosing of morphine at the bedside. This will maximize therapeutic efficacy while minimizing the likelihood of adverse events and reduce long-term side effects in the neonatal population. These important strides in improving patient safety will lead to better patient outcomes.

Division Publications

1. Darwich AS; Ogungbenro K; Vinks AA; Powell JR; Reny JL; Marsousi N; Daali Y; Fairman D; Cook J; Lesko LJ. **Why has model-informed precision dosing not yet become common clinical reality? lessons from the past and a roadmap for the future.** *Clinical Pharmacology and Therapeutics*. 2017; 101:646-656.

2. Ramsey LB; Mizuno T; Vinks AA; Margolis PA. **Learning Health Systems as Facilitators of Precision Medicine.** *Clinical Pharmacology and Therapeutics*. 2017; 101:359-367.

3. Vinks AA. **Precision Medicine-Nobody Is Average.** *Clinical Pharmacology and Therapeutics*. 2017; 101:304-307.

4. Downes KJ; Dong M; Fukuda T; Clancy JP; Haffner C; Bennett MR; Vinks AA; Goldstein SL. **Urinary kidney injury biomarkers and tobramycin clearance among children and young adults with cystic fibrosis: a population pharmacokinetic analysis.** *Journal of Antimicrobial Chemotherapy*. 2017; 72:254-260.

5. Yu T; Enioutina EY; Brunner HI; Vinks AA; Sherwin CM. **Clinical Pharmacokinetics and Pharmacodynamics of Biologic Therapeutics for Treatment of Systemic Lupus Erythematosus.** *Clinical Pharmacokinetics*. 2017; 56:107-125.

6. Marsh RA; Fukuda T; Emoto C; Neumeier L; Khandelwal P; Chandra S; Teusink-Cross A; Vinks AA; Mehta PA. **Pretransplant Absolute Lymphocyte Counts Impact the Pharmacokinetics of Alemtuzumab.** *Biology of Blood and Marrow Transplantation*. 2017; 23:635-641.

7. Khandelwal P; Emoto C; Fukuda T; Vinks AA; Neumeier L; Dandoy CE; El-Bietar J; Chandra S; Davies SM; Bleesing JJ. **A Prospective Study of Alemtuzumab as a Second-Line Agent for Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric and Young Adult Allogeneic Hematopoietic Stem Cell Transplantation.** *Biology of Blood and Marrow Transplantation*. 2016; 22:2220-2225.

8. Khandelwal P; Fukuda T; Mizuno K; Teusink-Cross A; Mehta PA; Marsh RA; Kashuba ADM; Vinks AA; Davies SM. **A Pharmacokinetic and Pharmacodynamic Study of Maraviroc as Acute Graft-versus-Host Disease Prophylaxis in Pediatric Allogeneic Stem Cell Transplant Recipients with Nonmalignant Diagnoses.** *Biology of Blood and Marrow Transplantation*. 2016; 22:1829-1835.

9. Miyake M; Minami T; Yamazaki H; Emoto C; Mukai T; Toguchi H. **Arachidonic acid with taurine enhances pulmonary absorption of macromolecules without any serious histopathological damages.** *European Journal of Pharmaceutics and Biopharmaceutics*. 2017; 114:22-28.

10. Mizuno T; Fukuda T; Christians U; Perentesis JP; Fouladi M; Vinks AA. **Population pharmacokinetics of temsirolimus and sirolimus in children with recurrent solid tumours: a report from the Children's Oncology Group.** *British Journal of Clinical Pharmacology*. 2017; 83:1097-1107.

11. 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.** *The Pharmacogenomics Journal*. 2017; 17:162-169.

12. Miyake M; Koga T; Kondo S; Yoda N; Emoto C; Mukai T; Toguchi H. **Prediction of drug intestinal absorption in human using the Ussing chamber system: A comparison of intestinal tissues from animals and humans.** *European Journal of Pharmaceutical Sciences*. 2017; 96:373-380.

13. Cvijanovich NZ; King JC; Flori HR; Gildengorin G; Vinks AA; Wong HR. **Safety and Dose Escalation Study of Intravenous Zinc Supplementation in Pediatric Critical Illness.** *Journal of Parenteral and Enteral Nutrition*. 2016; 40:860-868.

14. Hahn D; Emoto C; Vinks AA; Fukuda T. **Developmental Changes in Hepatic Organic Cation Transporter OCT1 Protein Expression from Neonates to Children.** *Drug metabolism and disposition: the biological fate of chemicals*. 2017; 45:23-26.

15. Balyan R; Zhang X; Chidambaran V; Martin LJ; Mizuno T; Fukuda T; Vinks AA; Sadhasivam S. **OCT1 genetic variants are associated with postoperative morphine-related adverse effects in children.** *Pharmacogenomics*. 2017; 18:621-629.

16. Balyan R; Mecoli M; Venkatasubramanian R; Chidambaran V; Kamos N; Clay S; Moore DL; Mavi J; Glover CD; Szmuk P. **CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients.** *Pharmacogenomics*. 2017; 18:337-348.

17. Chidambaran V; Pilipenko V; Spruance K; Venkatasubramanian R; Niu J; Fukuda T; Mizuno T; Zhang K; Kaufman K; Vinks AA. **Fatty acid amide hydrolase-morphine interaction influences ventilatory response to hypercapnia and postoperative opioid outcomes in children.** *Pharmacogenomics*. 2017; 18:143-156.

18. Chen Y; Lu J; Dong M; Wu D; Zhu Y; Li Q; Chen C; Li Z. **Target attainment analysis and optimal sampling designs for population pharmacokinetic study on piperacillin/tazobactam in neonates and young infants.** *European Journal of Clinical Pharmacology*. 2016; 72:1479-1488.

19. 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.** *Journal of Pediatric Psychology*. 2017; 42:jsw039.

20. Emoto C; Vinks AA; Fukuda T. **Risk Assessment of Drug-Drug Interactions of Calcineurin Inhibitors Affecting Sirolimus Pharmacokinetics in Renal Transplant Patients.** *Therapeutic Drug Monitoring*. 2016; 38:607-613.

21. Diwan TS; Lichvar AB; Leino AD; Vinks AA; Christians U; Shields AR; Cardi MA; Fukuda T; Mizuno T; Kaiser T. **Pharmacokinetic and pharmacogenetic analysis of immunosuppressive agents after laparoscopic sleeve gastrectomy.** *Clinical Transplantation*. 2017; 31:e12975.

22. Emoto C; Fukuda T; Johnson TN; Neuhoff S; Sadhasivam S; Vinks AA. **Characterization of contributing factors to variability in morphine clearance through PBPK modeling implemented with OCT1 transporter.** *CPT: Pharmacometrics and Systems Pharmacology*. 2017; 6:110-119.

23. Emoto C; Fukuda T; Mizuno T; Schniedewind B; Christians U; Adams DM; Vinks AA. **Characterizing the developmental trajectory of sirolimus clearance in neonates and infants.** *CPT: Pharmacometrics and Systems Pharmacology*. 2016; 5:411-417.

Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Alexander Vinks, PhD	Cincinnati Pediatric Clinical Pharmacology Postdoctoral Training Program	National Institutes of Health	T32 HD069054	05/01/2016 - 04/30/2021	$336,471
Total Annual Grant Award Dollars					**$336,471**