

Division Details

Division Data Summary

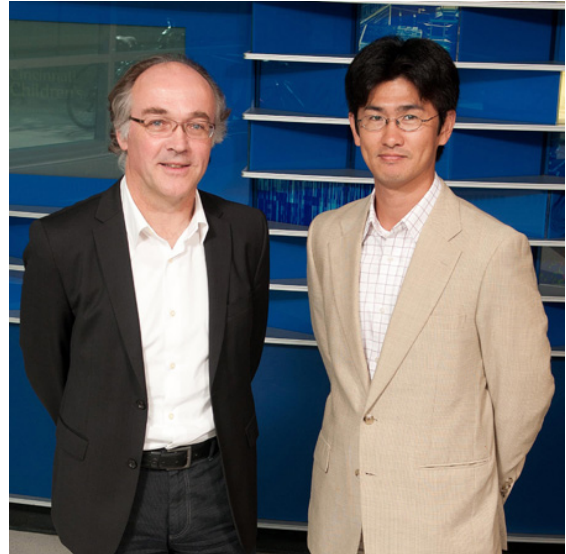
Research and Training Details

Number of Faculty	2
Number of Joint Appointment Faculty	3
Number of Research Fellows	4
Number of Research Students	4
Number of Support Personnel	3
Direct Annual Grant Support	\$190,836
Peer Reviewed Publications	10

Clinical Activities and Training

Number of Clinical Staff	1
Number of Clinical Fellows	5

Division Photo



Left to Right: S Vinks, T Fukuda

Significant Accomplishments

Personalized Therapeutics through Pharmacokinetics and Pharmacogenomics

Our research seeks to identify pharmacokinetic (PK), pharmacodynamic (PD) and pharmacogenetic (PGx) factors to explain differences in clinical response to drugs and adverse events in pediatric patients. One important focus area is immunomodulating therapies in transplantation. For decades clinicians have struggled with individualized dosing of drugs to improve clinical outcomes and reduce toxic side effects. With funding from a Place Outcome Award by The James M. Anderson Center for Health Systems Excellence, we worked with David Hooper, MD, and members of Nephrology, Biomedical Informatics, and the Adherence Center to develop a web-based therapeutic decision support system (dashboard) with a graphical user interface. The dashboard provides real-time views of individual patient data that are essential for the management of therapy and will alert providers of increased risk of toxicity and drug interaction potential. The novel dashboard includes pharmacogenetic information, pharmacokinetic summaries and real-time adherence data and is made available to providers to enhance their medication management decision making. We also continue to work with the Genetic Pharmacology Service, the first of its kind in a pediatric institution. Our research focuses on genotyping-phenotyping studies of neuropsychiatric drugs such as risperidone and warfarin.

Pharmacometrics and Quantitative Pharmacology

As part of the personalized pain initiative, we work with Anesthesia on novel pharmacological approaches that use the patient's drug metabolizing genotype and phenotype to manage pain with morphine and related drugs, reduce adverse events and avoid clinically significant drug/drug interactions. A successful joint effort includes a

study on the disposition of morphine and metabolites that identified important PGx factors in postsurgical patients that could help predict morphine's dose. This finding and its potential role in personalizing analgesia is currently being investigated in a larger cohort of patients. A joint effort with the Center for Bariatric Research and Innovation funded through the translational research initiative was the successful completion of a PK study of propofol in obese patients undergoing bariatric surgery and the development of an evidence based dosing algorithm. With the Cancer and Blood Diseases Institute, we successfully completed a PK-guided study of sirolimus in children with NF1 and plexiform neurofibromas. The results of the PK analysis have been submitted for publication. As part of the project we have initiated an in-vitro program studying the genetics and developmental aspects of sirolimus disposition. We now have identified the important metabolic pathways by which sirolimus is metabolized using both in adult and pediatric liver tissues.

T32 Program in Pediatric Clinical Pharmacology

We are one of three sites awarded a pediatric clinical and developmental pharmacology training grant (T32) from the National Institutes of Health. This postdoctoral program trains the next generation of clinical investigators to assume leadership roles in developing innovative approaches that will enhance pediatric therapeutics. Many medicines have not been scientifically evaluated for use in children and are either used unlicensed or in an off-label manner. In addition, far fewer medicines have been developed specifically to treat childhood diseases. One of our major goals is to provide research support and training that enhances the knowledge of residents, fellows and faculty about use of medications. We were fortunate to recruit two talented postdoctoral trainees, selected by the executive committee from a pool of high quality pediatric subspecialty trainee candidates. Dawn Pinchasik, MD, is a second year fellow in Pediatric Hematology-Oncology and Jason Wiles, MD, is a first year Neonatology fellow.

Division Highlights

The Division's mission is to conduct state-of-the-art Phase I - III clinical pharmacology studies that conform to GCP/ICH regulatory requirements in a safe, effective and timely fashion to produce new knowledge to enable optimal use of medications in newborns, children and adolescents. Our faculty is particularly interested in pharmacogenetics (PG), and population pharmacokinetic (PK)-pharmacodynamic (PD) modeling, and has extensive expertise in clinical trial design and simulation. We have ongoing studies investigating the pharmacokinetics (PK) and pharmacogenetics (PG) of sirolimus in patients with neurofibromatosis and vascular anomalies, the PK/PD and PG of mycophenolic acid (MMF, CellCept®) in transplant patients (with Nephrology), and in children with Lupus (with Rheumatology), propofol PK/PG dose optimization studies in morbidly obese patients, and personalized pain treatment with codeine and morphine (with Anesthesia and Surgery).

Alexander A. Vinks, PharmD, PhD

Dr. Vinks presided over the 12th International Congress of the International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IA-TDMCT) in Stuttgart, Germany. In his role as president he initiated clinical pharmacology and TDM related educational activities across the world by facilitating regional meetings in China, India and South America. As principal investigator of a Place Outcome Award by The James M. Anderson Center for Health Systems Excellence he and his collaborators in Nephrology, Biomedical Informatics and the Adherence Center developed a web-based therapeutic decision support system ('dashboard'). The dashboard provides real time views of individual patient data that are essential for the management of immunosuppressive therapy in transplantation and will alert providers of increased risk of toxicity and drug

interaction potential.

Tsuyoshi Fukuda, PhD

Dr. Fukuda authored five publications out of the Division's ongoing research on the Pharmacokinetics (PK) and Pharmacodynamics (PD) and Pharmacogenetics (PG) of Mycophenolate Mofetil in pediatric kidney transplant patients and childhood-onset Systemic Lupus Erythematosus (cSLE). In addition, his work was selected for presentation at the Annual meeting of the American Society of Clinical Pharmacology and Therapeutics, in Washington, DC and at the 12th International Congress of Therapeutic Drug Monitoring & Clinical Toxicology, in Stuttgart, Germany. He established a hand-on Pharmacometrics course for our clinical and postdoctoral fellows.

Division Publications

1. Cattaneo D, Vinks AA. **Optimizing immunosuppressive drug dosing in pediatric renal transplantation. Part of a special series on Paediatric Pharmacology, guest edited by Gianvincenzo Zuccotti, Emilio Clementi, and Massimo Molteni.** *Pharmacol Res.* 2012; 65:163-7.
2. Chidambaran V, Ngamprasertwong P, Vinks AA, Sadhasivam S. **Pharmacogenetics and anesthetic drugs.** *Curr Clin Pharmacol.* 2012; 7:78-101.
3. Fukuda T, Brunner HI, Sagcal-Gironella AC, Vinks AA. **Nonsteroidal anti-inflammatory drugs may reduce enterohepatic recirculation of mycophenolic acid in patients with childhood-onset systemic lupus erythematosus.** *Ther Drug Monit.* 2011; 33:658-62.
4. Hooper DK, Fukuda T, Gardiner R, Logan B, Roy-Chaudhury A, Kirby CL, Vinks AA, Goebel J. **Risk of tacrolimus toxicity in CYP3A5 nonexpressors treated with intravenous nicardipine after kidney transplantation.** *Transplantation.* 2012; 93:806-12.
5. Merhar SL, Schibler KR, Sherwin CM, Meinzen-Derr J, Shi J, Balmakund T, Vinks AA. **Pharmacokinetics of levetiracetam in neonates with seizures.** *J Pediatr.* 2011; 159:152-154 e3.
6. Sagcal-Gironella AC, Sherwin CM, Tirona RG, Rieder MJ, Brunner HI, Vinks AA. **Pharmacokinetics of prednisolone at steady state in young patients with systemic lupus erythematosus on prednisone therapy: an open-label, single-dose study.** *Clin Ther.* 2011; 33:1524-36.
7. Saldana SN, Hooper DK, Froehlich TE, Campbell KM, Prows CA, Sadhasivam S, Nick TG, Seid M, Vinks AA, Glauser TA. **Characteristics of successful recruitment in prospective pediatric pharmacogenetic studies.** *Clin Ther.* 2011; 33:2072-81.
8. Sherwin CM, Ding L, Kaplan J, Spigarelli MG, Vinks AA. **Optimal study design for pioglitazone in septic pediatric patients.** *J Pharmacokinet Pharmacodyn.* 2011; 38:433-47.
9. Sherwin CM, Sagcal-Gironella AC, Fukuda T, Brunner HI, Vinks AA. **Development of population PK model with enterohepatic circulation for mycophenolic acid in patients with childhood-onset systemic lupus erythematosus.** *Br J Clin Pharmacol.* 2012; 73:727-40.
10. Vinks AA. **Important role of population pharmacokinetic/pharmacodynamic modeling in pediatric therapeutics.** *J Pediatr.* 2011; 159:361-3.

Faculty, Staff, and Trainees

Faculty Members

Alexander A. Vinks, PharmD, PhD, Professor

Leadership Division Director; Fellowship Director; Co-Director, Genetic Pharmacology Service

Research Interests Population Pharmacokinetics, Pharmacokinetics, Pharmacodynamic (PK/PD) modeling, Pharmacogenetics/genomics, Clinical Trial Design and Simulation

Tsuyoshi Fukuda, PhD, Associate Professor

Research Interests Pharmacogenetics, Population PK/PD Modeling

Joint Appointment Faculty Members

Tracy A. Glauser, MD, Professor (Neurology)

Research Interests Pharmacogenetics/genomics, Epilepsy

Daniel W. Nebert, MD, Professor (Environmental Health and Center for Environmental Genetics)

Research Interests Pharmacogenetics/genomics

Siva Sivaganesan, PhD, Professor (Arts & Science, Mathematical Science)

Research Interests Population modeling and simulation

Clinical Staff Members

- **Shareen Cox, BS**,
Senior Research Assistant

Trainees

- **Min Dong, PhD**, 2010, University of Cincinnati
- **Raja Venkatasubramanian, PhD**, 2009, Merck & Company, West Point, PA
- **Tomoyuki Mizuno, PhD**, 2012, Kyoto University Hospital
- **Chie Emoto, PhD**, 2006, Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd.
- **Roeland Wasmann, MS candidate**, 2010, University of Groningen, the Netherlands
- **Elke Krekles, PhD candidate**, 2010, Leiden/Amsterdam Center for Drug Research
- **Marij deVries, MS candidate**, 2009, University of Groningen, the Netherlands
- **Jiraganya Bhongsatiern, PhD candidate**, 2010, University of Cincinnati
- **Andrea Hahn, MD**, 2008, Infectious Diseases, Cincinnati Children's Hospital Medical Center
- **Kevin Downes, MD**, 2008, Infectious Diseases, Cincinnati Children's Hospital Medical Center
- **Jason Wiles, MD**, 2008, Neonatology, Cincinnati Children's Hospital Medical Center
- **Dawn Pinchasik, MD**, 2007, Cancer & Blood Diseases Institute, Cincinnati Children's Hospital Medical Center
- **Edward Nehus, MD**, 2008, Nephrology, Cincinnati Children's Hospital Medical Center

Division Collaboration

Anesthesiology » Senthilkumar Sadhasivam, MD, MPH, Vidya Chidambaran, MD, and Pornswan Ngamprasertwong, MD

- Population PK/PD and pharmacogenetic studies of morphine in perioperative pain management.
- Propofol and remifentanyl in perinatal anesthesia.
- Development of a PK/PD model for propofol dose optimization in obese patients.

Behavioral Medicine & Clinical Psychology » Dennis Drotar, PhD and Ahna Pai, PhD

- Pharmacokinetics and pharmacogenetics of 6-mercaptopurine (6-MP) and metabolites in Acute Lymphoblastic Leukemia (ALL) as a marker for treatment adherence.
- Improving Safety and Efficacy of Mycophenolate Therapy – Development of a web-based therapeutic decision support system for adherence monitoring

Cancer & Blood Diseases Institute » John Perentesis, MD, Brian Weiss, MD, Maryam Fouladi, MD, Denise

Adams, MD, Parinda Mehta, MD, Dawn Pinchasik, MD, and Maureen O'Brien, MD

- A Phase-2 studies funded through the Department of Defense. Phase-I real time concentration - controlled clinical trial of sirolimus in patients with neurofibromatosis.
- A Phase 2 Study - Clinical Trial Assessing Efficacy and Safety of the mTOR Inhibitor Sirolimus in the Treatment of Complicated Vascular Anomalies.
- Phase I combination study of IMC-A12, a recombinant monoclonal antibody to the insulin-like growth factor receptor (IGFR) in combination with temsirolimus, an mTOR inhibitor in children and adolescents with recurrent or refractory solid tumors.
- Predictors of delayed Methotrexate Clearance During High-Dose Therapy.

Cardiology » David Cooper, MD, MPH

- Evaluation of the Pharmacokinetics of Recombinant ATIII in Neonates and Infants Undergoing CPB and ECMO Support.

Critical Care Medicine » Jennifer Kaplan, MD and Hector Wong, MD

- Pharmacokinetic/pharmacodynamic modeling and clinical trial design for Phase-1 study of PPAR antagonist pioglitazone in critically ill patients with sepsis.
- Pharmacokinetics of zinc supplementation in critically ill children.

Infectious Diseases » Margaret Hostetter, MD, Andrea Hahn, MD, and Kevin Downs, MD

- Pharmacogenomics of β -lactam Associated Neutropenia.
- Biomarkers for Acute Kidney Injury in patients with Cystic Fibrosis.

Neonatology » Henry Akinbi, MD and Jason Wiles, MD

- Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome

Nephrology; Acute Care Nephrology » Jens Goebel, MD, David Hooper, MD, Stuart Goldstein, MD, and Edward Nehus, MD

- Improving Safety and Efficacy of Mycophenolate Therapy – Development of a web-based therapeutic decision support system ('dashboard').
- Pharmacokinetics of meropenem, milrinone and fentanyl in critically ill patients during continuous renal replacement therapy (CRRT).
- PK/PD modeling and target attainment of meropenem during renal replacement therapy.

Neurology; Human Genetics ; Biomedical Informatics » Tracy Glauser, MD, Kejian Zhang, MD, Cynthia Prows, MSN, and John Pestian, PhD

- Genetic Pharmacology Service
- Development of pharmacogenetically guided dosing algorithms and decision support tools for treatment of epilepsy, neuropsychiatric drugs, warfarin and codeine.

Rheumatology » Hermine Brunner, MD, MS, Daniel J. Lovell, MD, MPH, and John B. Harley, MD, PhD

- Pharmacokinetic, pharmacogenetics and biomarker studies of mycophenolate and corticosteroids in patients with childhood onset Lupus.
- Infliximab and TNF blockade in JIA. Developing algorithms for individualized dosing.
- Developing pediatric pharmacogenetic applications in the Electronic Medical Records and Genomics (eMERGE) Network

- Surgery » Thomas H. Inge, MD, PhD
- TEENS-LAB ancillary study to develop of a PK/PD model for propofol dose optimization in bariatric surgery patients.

Grants, Contracts, and Industry Agreements

Grant and Contract AwardsAnnual Direct

VINKS, A			
Cincinnati Training Program in Pediatric Clinical and Developmental Pharmacology			
National Institutes of Health			
T32 HD 069054	05/16/11-04/30/16		\$187,836
Pilot Trial of Bumetanide for Neonatal Seizures			
National Institutes of Health(Children's Hospital Boston)			
R01 NS 066929	08/02/10-06/30/12		\$3,000
Current Year Direct			\$190,836

Service Collaborations

VINKS, A			
Pharm. Proj Solution			\$46,475
Current Year Direct			\$46,475

Funded Collaborative Efforts

VINKS, A			
Phase II Study of Rapamycin for Complicated Vascular Anomalies.			
Food and Drug Administration			
Adams, D	09/29/09-07/31/13		5%
Promoting Treatment Adherence in Adolescent Leukemia			
National Institutes of Health			
Drotar, D	09/28/07-07/31/12		5%
Cincinnati Multidisciplinary Clinical Research Center			
National Institutes of Health			
Lovell, D	08/01/07-07/31/13		3%
Total			\$237,311