

## Division Data Summary

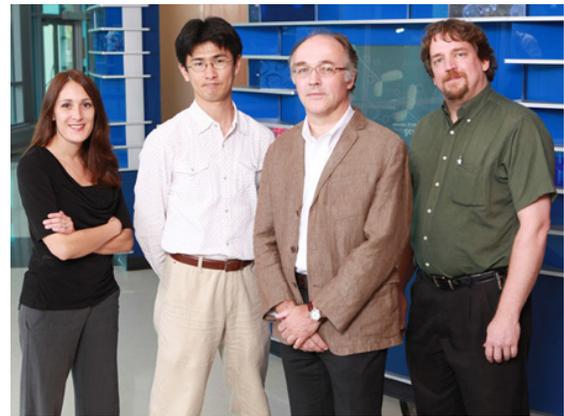
### Research and Training Details

Number of Faculty	3
Number of Joint Appointment Faculty	4
Number of Research Fellows	2
Number of Research Students	2
Number of Support Personnel	3
Direct Annual Grant Support	\$124,484
Peer Reviewed Publications	12

### Clinical Activities and Training

Number of Clinical Fellows	2
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## Division Photo



Left to Right: S Saldana, T Fukuda, S Vinks, M Spigarelli

## Significant Publications

Mehta PA, [Vinks AA](#), Filipovich A, Bleesing J, Jodele S, Jordan MB, Marsh R, Tarin R, Edwards S, Fearing D, Lawrence J, Davies SM. **Alternate-day micafungin antifungal prophylaxis in pediatric patients undergoing hematopoietic stem cell transplantation: a pharmacokinetic study.** *Biol Blood Marrow Transplant.* 16(10):1458-62. Oct, 2010.

Disseminated fungal infection is a major cause of morbidity and mortality in children undergoing hematopoietic stem cell transplantation (HSCT). Prophylaxis with amphotericin B can be limited by renal toxicity. Micafungin has several advantages including a better safety profile. We studied whether a higher dose micafungin every other day would provide drug exposure similar to standard daily dosing to improve patient adherence in very young children in whom oral medications can be challenging, at reduced administration costs. The results suggest that alternate day micafungin dosing may provide an attractive alternative for antifungal prophylaxis in HSCT patients and merits further evaluation.

Sherwin CM, Ding L, Kaplan J, [Spigarelli MG](#), [Vinks AA](#). **Optimal study design for pioglitazone in septic pediatric patients.** *J Pharmacokinet Pharmacodyn.* Jun 11, 2011.

The objective was to develop the methodology and process of optimal sparse sampling pharmacokinetics and trial design using modeling and simulation in a study in critically ill infants and children. The optimal design provided clinically attainable sample times and windows and was incorporated in an investigational new drug (IND) application to the FDA.

Merhar S, Schibler K, [Vinks AA](#). **Pharmacokinetics and safety of intravenous levetiracetam in the treatment of neonates with seizures.** *J Pediatr.* 159(1):152-154. Jul, 2011.

This is the first study on the pharmacokinetics of levetiracetam neonates with seizures. Neonates were found to have lower clearance, higher volume of distribution, and a longer half-life as compared to older children and adults. The results of the study provide a basis for better dosing of levetiracetam in this vulnerable population.

Gerlach LS, Saldaña SN, Wang Y, Nick TG, Spigarelli MG. **Retrospective review of the relationship between weight change and demographic factors following initial depot medroxyprogesterone acetate injection in adolescents.** *Clin Ther.* 33:182-187. 2011.

Depot medroxyprogesterone acetate (DMPA) is an effective contraceptive administered by intramuscular injection every 3 months. DMPA is an increasingly popular contraceptive choice for adolescents, yet its use is associated with weight gain as well as subsequent non-adherence and long-term obesity-related diseases and mortality. This study evaluated the relationship between weight change at 10 to 14 weeks post-DMPA initiation and race, baseline weight, and gynecologic age in female adolescents. We found that race, gynecologic age, and baseline weight are not associated with weight gain 10 to 14 weeks following initiation of DMPA.

## Division Highlights

### 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 in the pharmacogenetics (PG) of warfarin, and risperidone, the PK/PD and PG of mycophenolic acid (MMF, CellCept®) in transplant patients (with Nephrology), and in children with Lupus (with Rheumatology), and propofol PK/PG dose optimization studies in morbidly obese patients (with Anesthesia and Surgery).

### Alexander A. Vinks, PharmD, PhD

Dr. Vinks was awarded the first pediatric T32 training grant in Clinical and Developmental Pharmacology from NICHD to train the next generation of pediatric clinical pharmacologists. Dr. Vinks also serves as president of the International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IA-TDMCT). In this role 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 TEENS-LAB ancillary pharmacokinetic, pharmacodynamic and pharmacogenetics study of propofol in morbidly obese patients he and his team successfully completed this study. The project was supported by the translational research initiative (TRI). The purpose of the study is to develop a personalized dosing algorithm for propofol use in bariatric surgery patients.

### Tsuyoshi Fukuda, PhD

Dr. Fukuda was invited for presentation 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) at a FDA expert meeting on biomarker development. In addition, his work was selected for presentation at the Annual meeting of the American Society of Clinical Pharmacology and Therapeutics (Dallas, March 2011) and at Showa Pharmaceutical University in Japan.

### Shannon N. Saldaña, PharmD, MS

Dr. Saldaña completed her warfarin pharmacogenetic study supported by a T1 Translational Research Award through the University of Cincinnati Center for Clinical and Translational Science (CCTST). The goal is to

develop a pediatric warfarin dosing algorithm that incorporates clinical information and CYP2C9 and VKORC1 genotypes. She also completed her pharmacokinetics and pharmacogenetic study in risperidone-treated children and adolescents with psychiatric or neurodevelopmental disorders with support from the Clinical Research Feasibility Funds Program (CREFF). This work builds on risperidone studies performed by our PPRU in the past. The results will be used to design a proof-of-concept prospective trial to test PK/PG-guided dosing in psychiatric patients initiated on risperidone treatment.

### **Michael G. Spigarelli, MD, PhD**

Dr. Spigarelli served as the chair of the Special Population Section of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) and as a board member of the American Board of Clinical Therapeutics chairing the Certification Examination Subcommittee responsible for designing and administering the national certification examination. He also serves as the chair of the Adolescent Prioritization Committee for the Best Pharmaceuticals for Children Act (BPCA). His research involves a variety of different projects from directing the Cincinnati Genomic Control Cohort Project to working to understand the role adverse events such as weight gain and hormonal imbalance play in susceptible individuals and how that can provide insight regarding the underlying physiologic and pharmacologic mechanisms involved.

## Division Collaboration

**Anesthesiology** » Senthilkumar Sadhasivam, MD; Vidya Chidmabaran, MD; Pornswan Ngamprasertwong, MD  
Population PK/PD and pharmacogenetic studies of morphine in perioperative pain management, and propofol and remifentanyl in perinatal anesthesia. Development of a PK/PD model for propofol dose optimization in obese patients.

**Nephrology; Acute Care Nephrology** » Jens Goebel, MD; David Hooper, MD; Stuart Goldstein, MD  
Pharmacokinetics, pharmacogenetics and biomarker studies of mycophenolate-mofetil (MMF, CellCept) in kidney transplant patients supported by the NIH. Developing algorithms for individualized dosing. PK of meropenem, milrinone and fentanyl in critically ill patients during continuous renal replacement therapy (CRRT).

**Neurology; Human Genetics; Biomedical Informatics** » Tracy Glauser, MD; Kejian Zhang, MD; Cynthia A. Prows, MSN; John Pestian, PhD  
Genetic Pharmacology Service and development of pharmacogenetically guided dosing algorithms and decision support tools for treatment of epilepsy, neuropsychiatric drugs and warfarin.

**Rheumatology** » Hermine Brunner; Daniel J. Lovell, MD, MPH  
Pharmacokinetic, pharmacogenetics and biomarker studies of mycophenolate-mofetil (MMF, CellCept) and corticosteroids in patients with Lupus. Infliximab and TNF blockade in JIA. Developing algorithms for individualized dosing.

**Behavioral Medicine & Clinical Psychology** » Dennis Drotar, PhD; Ahna Pai, PhD  
Pharmacokinetics and pharmacogenetics of 6-mercaptopurine (6-MP) and metabolites in Acute Lymphoblastic Leucemia (ALL) as a marker for treatment adherence. Non-adherence can result in less than optimal concentrations of 6MP which are associated with poor disease prognosis in children with ALL. Application of population pharmacokinetic modeling techniques to help study adherence to immunosuppressive and antiepileptic medical regimens, including the measurement of adherence and identifying barriers to effective disease management as well as health-related quality of life.

**Cancer & Blood Diseases** » John Perentesis, MD; Brian Weiss, MD; Maryam Fouladi, MD; Denise Adams, MD  
A Phase-2 studies funded through the Department of Defense. Phase-I real time concentration - controlled clinical trail 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.

**Surgery; Fetal Surgery** » Thomas H. Inge, MD; Timothy Crombleholme, MD  
TEENS-LAB ancillary study to develop of a PK/PD model for propofol dose optimization in bariatric surgery patients. PK/PD optimization of nifedipine in twin twin transfusion syndrome (TTTS).

**Neonatology** » Stephanie Merhar, MD; Kurt Schibler, MD  
Pharmacokinetics and dose finding study of levetiracetam in neonates. There is a pressing need to find better medications for the treatment of neonatal seizures. Levetiracetam is a relatively new antiepileptic drug that has many pharmacokinetic characteristics that are considered “ideal”. This is one of the first pharmacokinetic studies of levetiracetam in preterm and term neonates.

**Critical Care Medicine** » Jennifer Kaplan, MD; Hector Wong, MD  
Pharmacokinetic/pharmacodynamic modeling and clinical trial design for Phase-1 study of PPAR antagonist pioglitazone in critically ill patients with sepsis.

## Faculty Members

**Alexander A. Vinks, PharmD, PhD**, Professor

*Director*

*Fellowship director*

**Research Interests** Population Pharmacokinetics, Pharmacodynamics (PK/PD), Pharmacogenetics/genomics, Clinical Trial Simulation

**Tsuyoshi Fukuda, PhD**, Associate Professor

**Research Interests** Pharmacogenetics, Population PK/PD Modeling

**Shannon N. Saldaña, PharmD, MS**, Assistant Professor

**Research Interests** Pharmacogenetics, Psychopharmacology

## 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

**Michael G. Spigarelli, MD, PhD**, Associate Professor

Adolescent Medicine

**Research Interests** Clinical Pharmacology, Clinical trials

## Trainees

- Ebian Brill, MS, 2010, University of Groningen, The Netherlands
- Marianne Kuijvenhoven, MS, 2009, University of Groningen, The Netherlands
- Catherine Sherwin, PhD, 2007, University of Otago, Dunedin, New Zealand
- Jing Shi, MD, PhD, 2006, West China Second University Hospital, Sichuan, Chi na

## Significant Accomplishments

### **NIH Training Grant**

We were awarded the first pediatric clinical and developmental pharmacology training grant (T32) from the National Institutes of Health. This postdoctoral program will train 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.

### **Individualized Therapies in Transplantation, Rheumatology and Anesthesiology**

Our investigators seek to better understand the dose-concentration-response and adverse-events relationships of immunosuppressive drugs in pediatric patients receiving organ transplants. Immune suppressing therapies have led to unprecedented short-term patient and graft survival, but long-term survival rates remain suboptimal. Our ongoing research, funded through the National Institutes of Health and other sources, seeks to identify pharmacokinetic, pharmacodynamic and pharmacogenetic factors to explain differences in adverse events and clinical response in transplant patients. Our work includes studying the age-dependent disposition of mycophenolic acid in pediatric renal transplant recipients and children with lupus using newly discovered genetic polymorphisms. Our data will help develop web-based “dashboards” and dosing algorithms to allow personalized dose tailoring.

We also have finalized an important study in morbidly obese adolescents identifying pharmacokinetic, pharmacodynamic and pharmacogenetic factors that will allow personalized propofol anesthesia during bariatric surgery. As part of our personalized pain initiative, we work with colleagues in the Department of 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.

### **Pharmacometrics and Genetic Pharmacology Programs**

A pharmacometrics program was established to provide an academic training program that enables students, fellows and junior faculty to gain expertise in pharmacokinetic/pharmacodynamic modeling and simulation as part of clinical trial design, data analysis and individualized dosing algorithm development. Several clinical faculty and students from across the medical campus participate in the program.

We also continue to work with the Genetic Pharmacology Service, the first of its kind in a pediatric institution. This service is a first step toward personalized medicine for neuropsychiatric and anticoagulation drug therapy. Our research focuses on genotyping-phenotyping studies of neuropsychiatric drugs such as

risperidone and warfarin. We develop computerized decision support systems that integrate evidence-based medicine, patient genotypes and phenotypes, as well as drug pharmacology and environmental factors.

## Division Publications

1. Brandhorst G, Oellerich M, Brunet M, Kowalski R, Vinks A, Wallemacq P. **Individually tailored immunosuppression: is there a role for biomarkers?**. *Clin Chem*. 2011; 57:376-81.
2. Fukuda T, Goebel J, Thogersen H, Maseck D, Cox S, Logan B, Sherbotie J, Seikaly M, Vinks AA. **Inosine monophosphate dehydrogenase (IMPDH) activity as a pharmacodynamic biomarker of mycophenolic acid effects in pediatric kidney transplant recipients**. *J Clin Pharmacol*. 2011; 51:309-20.
3. Gerlach LS, Saldana SN, Wang Y, Nick TG, Spigarelli MG. **Retrospective review of the relationship between weight change and demographic factors following initial depot medroxyprogesterone acetate injection in adolescents**. *Clin Ther*. 2011; 33:182-7.
4. Harris E, Eng HY, Kowatch R, Delgado SV, Saldana SN. **Disinhibition as a side effect of treatment with fluvoxamine in pediatric patients with obsessive-compulsive disorder**. *J Child Adolesc Psychopharmacol*. 2010; 20:347-53.
5. Li Z, Wang L, Wang Y, Gui YH, Vinks AA, MacLeod S. **Better medicines for 300 million children in China: report on recent progress**. *Paediatr Drugs*. 2011; 13:137-40.
6. Mehta PA, Vinks AA, Filipovich A, Bleesing J, Jodele S, Jordan MB, Marsh R, Tarin R, Edwards S, Fearing D, Lawrence J, Davies SM. **Alternate-day micafungin antifungal prophylaxis in pediatric patients undergoing hematopoietic stem cell transplantation: a pharmacokinetic study**. *Biol Blood Marrow Transplant*. 2010; 16:1458-62.
7. Sagcal-Gironella AC, Fukuda T, Wiers K, Cox S, Nelson S, Dina B, Sherwin CM, Klein-Gitelman MS, Vinks AA, Brunner HI. **Pharmacokinetics and pharmacodynamics of mycophenolic acid and their relation to response to therapy of childhood-onset systemic lupus erythematosus**. *Semin Arthritis Rheum*. 2011; 40:307-13.
8. Sherwin CM, Fukuda T, Brunner HI, Goebel J, Vinks AA. **The evolution of population pharmacokinetic models to describe the enterohepatic recycling of mycophenolic acid in solid organ transplantation and autoimmune disease**. *Clin Pharmacokinet*. 2011; 50:1-24.
9. Soldin OP, Soldin SJ, Vinks AA, Younis I, Landy HJ. **Longitudinal comparison of thyroxine pharmacokinetics between pregnant and nonpregnant women: a stable isotope study**. *Ther Drug Monit*. 2010; 32:767-73.
10. Tett SE, Saint-Marcoux F, Staatz CE, Brunet M, Vinks AA, Miura M, Marquet P, Kuypers DR, van Gelder T, Cattaneo D. **Mycophenolate, clinical pharmacokinetics, formulations, and methods for assessing drug exposure**. *Transplant Rev (Orlando)*. 2011; 25:47-57.
11. Tonshoff B, David-Neto E, Ettenger R, Filler G, van Gelder T, Goebel J, Kuypers DR, Tsai E, Vinks AA, Weber LT, Zimmerhackl LB. **Pediatric aspects of therapeutic drug monitoring of mycophenolic acid in renal transplantation**. *Transplant Rev (Orlando)*. 2011; 25:78-89.
12. Vinks AA, Saldana SN. **Developmental principles of pharmacokinetics**. *Pediatric psychopharmacology : principles and practice*. New York: Oxford University Press; 2010: 38-49. .

## Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct / Project Period Direct

VINKS, A

**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

**Cincinnati Training Program in Pediatric Clinical and Developmental Pharmacology**

National Institutes of Health

T32 HD 069054

05/16/11-04/30/16

\$121,484

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**Current Year Direct**

**\$124,484**

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**Total**

**\$124,484**