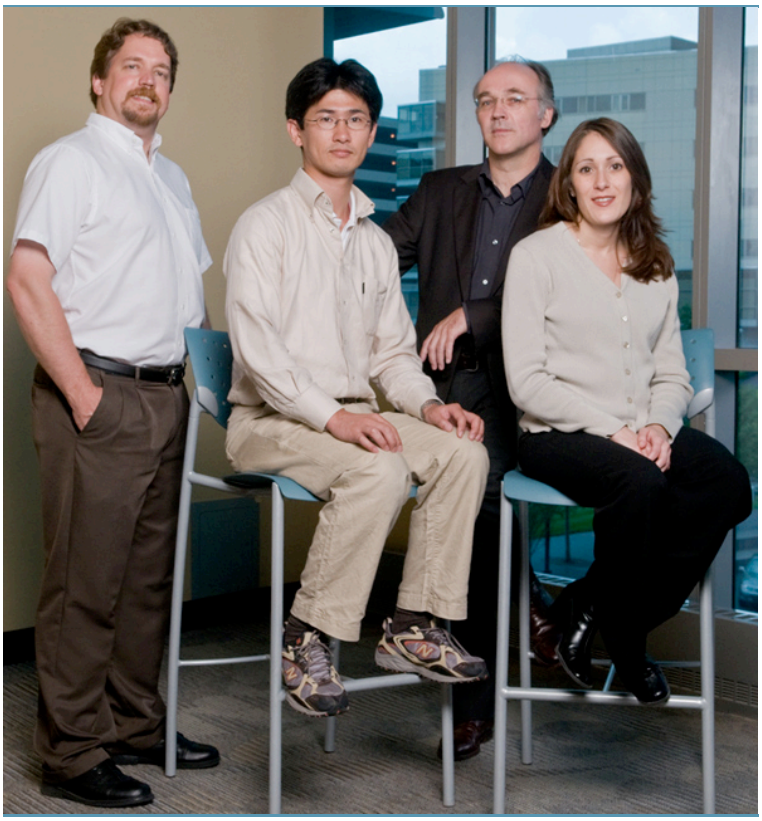
Clinical Pharmacology

Division Photo



Division Data Summary

Research and Training Details

Number of Faculty	3
Number of Joint Appointment Faculty	5
Number of Research Fellows	2
Number of Research Students	2
Number of Support Personnel	4
Direct Annual Grant Support	$392,294
Direct Annual Industry Support	$197,859
Peer Reviewed Publications	12

Significant Publications

Prausa SE, Fukuda T, Maseck D, Curtsinger KL, Liu C, Zhang K, Nick TG, Sherbotie JR, Ellis EN, Goebel J, Vinks AA. (2009). UGT genotype may contribute to adverse events following medication with mycophenolate mofetil in pediatric kidney transplant recipients. Clin Pharmacol Ther 85, 495-500.

Leukopenia and diarrhea are the predominant adverse events associated with mycophenolate mofetil (MMF, CellCept)), leading to dose reduction or discontinuation in children. Polymorphisms of the drug's main metabolizing enzyme, uridine diphosphate-glucuronosyl transferase (UGT), confer alteration in drug exposure. We studied the

incidence of these polymorphisms in pediatric kidney transplant recipients experiencing MMF-associated leukopenia and diarrhea. UGT genotypes of 16 affected children who recovered after MMF dose reduction or discontinuation were compared with those of 22 children who tolerated the drug at standard doses. All patients who were homozygous for UGT1A9 -331T>C developed leukopenia, and heterozygotes also had significantly more toxicity. A weaker association existed in UGT2B7 -900G>A carriers. Our data implicate UGT polymorphisms associated with altered drug exposure as potential predictors of adverse events when starting on MMF therapy.

Pestian J, Spencer M, Matykiewicz P, Zhang K, Vinks AA and Glauser T (2009) Personalizing drug selection using advanced clinical decision support. Biomedical Informatics Insights 2:19-29.

This article describes the process of developing an advanced pharmacogenetics clinical decision support at one of the United States' leading pediatric academic medical centers. This system, called CHRISTINE, combines clinical and genetic data to identify the optimal drug therapy when treating patients with epilepsy or Attention Deficit Hyperactivity Disorder. A description of clinical decision support systems is provided, along with an overview of neurocognitive computing and how it is applied in this setting.

The results presented provide a basis for ongoing studies as part of the Genetic Pharmacology Program.

Division Highlights

Tsuyoshi Fukuda, PhD

Dr. Fukuda who was a visiting scientist from Japan was recruited as a fcaulty member to further develop the division's pharmacogenetics program. He was instrumental in the pharmacogenetic studies of the anti-rejection medication mycophenolate-mofetil (MMF, CellCept) to show that renal transplant patients with a specific mutation in the UGT gene that helps breakdown the drug are at higher risk of developing leucopenia. The findings of the study where published in the Nature journal Clinical Pharmacology and Therapeutics.

Shannon N. Saldaña, PharmD, MS

Dr. Saldaña successfully finalized her translational research initiative (TRI) funded project studying the relationships between pharmacogenetic markers and the pharmacokinetics and drug exposure-response (efficacy and toxicity) of risperidone (Risperdal®) in children and adelescent with neuropsychiatric disorders. This work builds on previous risperidone studies performed by our PPRU. The results will be used to design a proof-of-concept prospective trial to test a dosing algorithm in a small cohort of psychiatric patients initiated on risperidone treatment.

Alexander A. Vinks, PharmD, PhD

Dr. Vinks received a translational research initiative (TRI) grant to study the pharmacokinetics, pharmacodynamics and pharmacogenetics of propofol, a commonly used anesthetic drug in morbidly obese patients. The purpose of the study is to develop an individualized dosing algorithm for use in bariatric surgery patients.

Division Collaboration

Collaboration with Neurology; Human Genetics; Biomedical Informatics

Collaborating Faculty: Tracy A. Glauser, MD; Diego A. Morita, MD; Kejian Zhang, MD, MBA; Cynthia A. Prows, MSN; John Pestian

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

Collaboration with Nephrology and Hypertension

Collaborating Faculty: Jens Goebel, MD; David Hooper

Pharmacokinetics, pharmacogenetics and biomarker studies of mycophenolate-mofetil (MMF, CellCept) in kidney transplant patients supported by the NIH. Developing algorithms for individualized dosing.

Collaboration with Hematology/Oncology

Collaborating Faculty: John P. Perentesis, MD; Brian D. Weiss, MD; Nancy Ratner, PhD; Timothy P. Cripe, MD, PhD

Clinical Pharmacology Core in national Neurofibromatosis Consortium studies funded through the Department of Defense. Phase-I real time concentration - controlled clinical trail of sirolimus in patients with neurofibromatosis.

Collaboration with Rheumatology

Collaborating Faculty: Hermine Brunner, MD; Daniel J Lovell, MD, MPH; Anna Carmella Sagcal, MD

Pharmacokinetic, pharmacogenetics and biomarker studies of mycophenolate-mofetil (MMF, CellCept) in patients

with Lupus. Infliximab and TNF blockade in JIA. Developing algorithms for individualized dosing.

Collaboration with Anesthesiology; Surgery

Collaborating Faculty: Senthilkumar Sdahasivam, MD, MPH; Vidya Chidambaran, MD; Thomas H. Inge, MD, PhD

Pharmacogenetic studies of morphine in perioperative pain management. Development of a PK/PD model for propfol dose optimization

Collaboration with Critical Care Medicine

Collaborating Faculty: Hector R. Wong, MD

Pharmacokinetic/pharmacodynamic modeling and trial simulation of zinc to inform the optimal design of a large randomized, placebo controlled efficacy trial. While the role of zinc homeostasis/supplementation has not been well-studied in critically ill children, it stands to reason that abnormal zinc homeostasis can be detrimental to the course of critical illness in children, and consequently, that zinc supplementation may be a cost effective and beneficial therapeutic strategy.

Collaboration with Neonatology

Collaborating Faculty: Kurt R. Schibler, MD; Stephanie Merhar, MD

Pharmacokinetics and dose finding study of leveteracetam 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 leveteracetam in preterm and term neonates.

Collaboration with Behavioral Medicine and Clinical Psychology

Collaborating Faculty: Dennis Drotar, PhD; Ahna Pai, PhD; Avani C. Modi, PhD

Pharmacokinetic s and pharmacogenetics of 6-mercaptopurine (6MP) 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 antiepilepric medical regimens, including the measurement of adherence and identifying barriers to effective disease management as well as health-related quality of life.

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, Research Associate Professor
Research Interests: Pharmacogenetics, Population PK/PD Modeling

Shannon N. Saldaña, PharmD, MS, Instructor Clinical
Research Interests: Pharmacogenetics, Psychopharmacology

Joint Appointment Faculty Members

Tracy A. Glauser, MD, Professor
Neurology
Pharmacogenetics/genomics, Epilepsy

Daniel W. Nebert, MD, Professor
Environmental Health and Center for Environmental Genetics
Pharmacogenetics/genomics

Siva Sivaganesan, PhD, Professor
Arts & Science, Mathematical Science
Population modeling and simulation

Michael G. Spigarelli, MD, PhD, Assistant Professor
Adolescent Medicine
Clinical Pharmacology, Clinical trials

Trainees

- **Sanne de Ridder, MS,** 2008, Leiden University, Leiden, 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

Pediatric Clinical Pharmacology

The Pediatric Pharmacology Research Unit (PPRU), under the direction of Alexander Vinks, PharmD, PhD, is one of just 13 units across the United States established by the National Institute of Child Health and Human Development in response to the need for appropriate drug therapy for pediatric patients (www.ppru.org). Its mission is to conduct 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. The PPRU staff at Cincinnati Children's is particularly interested in pharmacogenetics (PG), and population pharmacokinetic (PK)-pharmacodynamic (PD) modeling, and has extensive expertise in clinical trial design and simulation. Our unit is the lead site for several studies ranging from specific drug class evaluations (e.g. antiepileptic drugs in a NINDS Childhood Absence Study with Neurology), pharmacogenetics (e.g. mycophenolic acid (MMF, CellCept®) in transplant patients with Nephrology, and in children with Lupus, with Rheumatology), and pharmacokinetics-pharmacodynamics, safety and efficacy studies (e.g. propofol (Diprivan®) dose optimization in morbidly obese patients, with Anesthesia and Surgery).

Immunomodulation Studies

There exists an unmet clinical need to better understand the dose-concentration-response and adverse events relationships of immunosuppressive drugs in pediatric patients. Immunosuppressive combination therapy has led to unprecedented patient and graft survival over the near term, but long-term survival of patients and grafts are still suboptimal. The central hypothesis for our ongoing research funded through the NIH and other mechanisms is that differences in adverse events and clinical response in transplant patients are associated with identifiable pharmacokinetic (PK), pharmacodynamic (PD) and pharmacogenetic/genomic factors. Using validated pharmacokinetic, biomarker and sequencing assays our studies are designed to address the current information gap regarding age dependent disposition of mycophenolic acid (MMF, CellCept®) in pediatric renal transplant recipients and children with Lupus using newly discovered genetic polymorphisms. Our data are instrumental in the development of computer model-based Bayesian dosing algorithms to allow personalized tailoring of the dose to each patient's needs.

Pharmacogenetics/Genomics

The division is actively involved in the Genetic Pharmacology Service , the first of its kind in a pediatric institution. The clinical service focuses on reducing adverse effects of commonly used medications (spanning multiple diseases and disorders) by identifying genetically determined variations in drug metabolism, providing patient specific dosing recommendations based on the patient's drug metabolizing genotype/phenotype and delineating clinically significant drug/drug interactions. The service will help clinicians determine how patients will respond to certain prescribed medications. This is a first step towards personalized medicine of neuropsychiatric and anticoagulation drug therapy. Our research is focused on genotyping-phenotyping studies of neuropsychiatric drugs such as risperidone and warfarin and the development of computerized decision support systems that integrates evidence based medicine, a patient's specific genotype, a patient's phenotype, basic and advanced drug pharmacology and environmental factors. The algorithms are designed to help physicians in selecting the best medication dose for a particular patient.

Division Publications

1. Hillman JB, Spigarelli MG. **"Sexuality: its development and direction."** *Developmental-behavioral pediatrics.* Philadelphia: Saunders Elsevier; 2009: 415-425.
2. Kato M, Fukuda T, Wakeno M, Okugawa G, Takekita Y, Serretti A, Azuma J, Kinoshita T. **[5-HT1A gene polymorphisms contributed to antidepressant response in major depression].** *Nihon Shinkei Seishin Yakurigaku Zasshi.* 2009; 29: 23-31.
3. Yamamoto A, Nonen S, Fukuda T, Yamazaki H, Azuma J. **Genetic polymorphisms of glycine N-acyltransferase in Japanese individuals.** *Drug Metab Pharmacokinet.* 2009; 24: 114-7.
4. Kato M, Fukuda T, Wakeno M, Okugawa G, Takekita Y, Watanabe S, Yamashita M, Hosoi Y, Azuma J, Kinoshita T, Serretti A. **Effect of 5-HT1A gene polymorphisms on antidepressant response in major depressive disorder.** *Am J Med Genet B Neuropsychiatr Genet.* 2009; 150B: 115-23.

5. Pestian J, Spencer M, Matykiewicz P, Zhang K, Vinks S, Glauser T. Personalizing drug selection using advanced clinical decision support. *Biomed Inform Insight.* 2009; 2: 19-29.
6. Prows CA, Saldana SN. Nurses' genetic/genomics competencies when medication therapy is guided by pharmacogenetic testing: children with mental health disorders as an exemplar. *J Pediatr Nurs.* 2009; 24: 179-88.
7. Glickman M, Nick TG, Saldaña SN. Pharmacogenetics and pharmacogenomics: Statistical challenges in design and analysis. *CHANCE.* 2009; 22: 56-62.
8. Prausa SE, Fukuda T, Maseck D, Curtsinger KL, Liu C, Zhang K, Nick TG, Sherbotie JR, Ellis EN, Goebel J, Vinks AA. UGT genotype may contribute to adverse events following medication with mycophenolate mofetil in pediatric kidney transplant recipients. *Clin Pharmacol Ther.* 2009; 85: 495-500.
9. Saez-Llorens X, Yogev R, Arguedas A, Rodriguez A, Spigarelli MG, De Leon Castrejon T, Bomgaars L, Roberts M, Abrams B, Zhou W, Looby M, Kaiser G, Hamed K. Pharmacokinetics and safety of famciclovir in children with herpes simplex or varicella-zoster virus infection. *Antimicrob Agents Chemother.* 2009; 53: 1912-20.
10. Thompson PA, Allen CE, Horton T, Jones JY, Vinks AA, McClain KL. Severe neurologic side effects in patients being treated for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2009; 52: 621-5.
11. Spigarelli MG. Adolescent participation in research. *J Adolesc Health.* 2008; 43: 1-2.
12. Wakeno M, Kato M, Okugawa G, Fukuda T, Hosoi Y, Takekita Y, Yamashita M, Nonen S, Azuma J, Kinoshita T. The alpha 2A-adrenergic receptor gene polymorphism modifies antidepressant responses to milnacipran. *J Clin Psychopharmacol.* 2008; 28: 518-24.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

VINKS, A

Optimizing MMF Therapy in Pediatric Transplant Patients
National Institutes of Health
K24 HD 050387 — 04/13/06 - 03/31/11 — $131,932 / $649,258

CCHMC Pediatric Pharmacology Research Unit
National Institutes of Health
U10 HD 37249 (supplement) — 01/01/08 - 12/31/09 — $100,984 / $100,984

Neurofibromatosis Consortium Development Operation PK Ctr STOPN
U.S. Department of Defense (Army) (University of Alabama at Birmingham)
W81XWH-05-1-0615 — 07/01/08 - 06/30/09 — $67,840 / $67,840

SPIGARELLI, M

Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Oseltamivir (Tamiflu) for the Treatment of Children Less than 24 Months of Age with Confirmed Influenza Infection
National Institutes of Health (University of Alabama at Birmingham)
N01 AI 030025 — 10/01/07 - 07/31/10 — $91,538 / $188,691

Current Year Direct **392,294**

Industry Contracts

Vinks, A

Roche Laboratories, Inc.	$ 180,832
Pfizer, Inc.	$ 15,400

Walson, P

Sciele Pharma Inc.	$ 1,627

Current Year Direct Receipts **$ 197,859**

Current Year Direct **0**

Funded Collaborative Efforts

VINKS, A

Improved Understanding of the Biology and Use of TNF Inhibition in Children with JRA
National Institutes of Health

Glass/Lovell	08/01/07 - 07/31/13	3 %

Promoting Treatment Adherence in Adolescent Leukemia
National Institutes of Health

Drotar	09/28/07 - 07/31/12	5 %

Child Policy Research Center
National Institutes of Health

Simpson	01/06/09 - 09/29/10	2 %

Cincinnati Center of Neurofibromatosis Research
National Institutes of Health

Ratner	09/15/08 - 06/30/13	6 %

Centers for Education in Research and Therapeutics (CERT)
Agency for Healthcare Research and Qualilty

Lannon	09/01/07 - 08/31/11	1 %

SALDANA, S

Centers for Education in Research and Therapeutics (CERT)
National Institutes of Health

Lannon	09/01/07 - 08/31/11	11 %

SPIGARELLI, M

Clinical Translational Sciences Award
National Institutes of Health

Heubi	04/03/09 - 03/31/14	10 %

Total $ 590,513