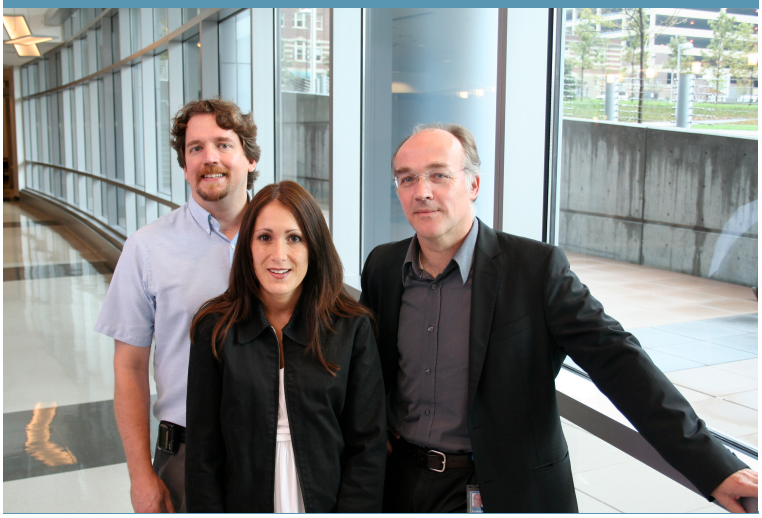
Clinical Pharmacology

Division Photo



Left to right: M.Spigarelli, S. Saldaña, S. Vinks

Division Data Summary

Research and Training Details

Number of Faculty	2
Number of Joint Appointment Faculty	5
Number of Research Fellows	2
Number of Research Students	2
Number of Support Personnel	5
Direct Annual Grant Support	$342,613
Direct Annual Industry Support	$72,687
Peer Reviewed Publications	7

Faculty Members

Alexander A. Vinks, PharmD, PhD, Professor ; *Director ; Fellowship director*
Research Interests: Population pharmacokinetics, pharmacodynamics, pharmacogenetics/genomics, clinical trial simulation

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

Philip D. Walson, MD, Professor
Clinical Pharmacology
Clinical trials

Trainees

- **Tsuyoshi Fukuda, PhD,** 2000, Osaka University, Osaka, Japan
- **Jing Shi, MD, PhD,** 2006, West China Second University Hospital, Sichuan, China
- **Havard Thogersen, MS,** 2007, Oslo University, Oslo, Norway
- **Sanne de Ridder, MS,** 2008, Leiden University, Leiden, the Netherlands

Significant Accomplishments in FY08

Clinical Pharmacology

Under the direction of Alexander Vinks, PharmD, PhD, the Pediatric Pharmacology Research Unit (PPRU) 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 - IV clinical pharmacology trials that conform to GCP/ICH regulatory requirements in a safe, effective and timely fashion to produce data that enables expanded labeling of drugs for pediatric patients. The PPRU staff at Cincinnati Children's is particularly interested in pharmacogenetics (PG), population pharmacokinetic (PK)-pharmacodynamic (PD) modeling, and has extensive expertise in clinical trial design and simulation. Our unit is the lead site for five studies ranging from specific drug class evaluations (e.g. antiepileptic drugs in the Childhood Absence Study with Neurology), pharmacogenetics (e.g. mycophenolic acid in transplant patients with Nephrology), and pharmacokinetics, safety and efficacy studies (e.g. lorazepam sedation with Critical Care).

Immunomodulation

There exists an unmet clinical need to better understand the dose-concentration-response and adverse events relationships of immunosuppressive drugs in pediatric transplant patients. Immunosuppressive combination therapy has led to lower rates of acute rejection and 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 inter-patient variability in drug exposure, adverse events and clinical response in kidney transplant patients is 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 its impact on the exposure-response and toxicity using newly discovered genetic polymorphisms. Our data are being used to develop computer model-based Bayesian dosing algorithms to allow personalized tailoring of the dose to each patient's needs.

http://www.cincinnatichildrens.org/health/subscribe/horizons/archives/2005/2005-1/vinks.htm

Pharmacogenetics/Genomics of Neuropsychiatric Drugs

The division was instrumental in establishing a Genetic Pharmacology Service, the first of its kind in a pediatric institution. The clinical service focuses on reducing adverse effects of 52 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 drug therapy. Our research is centered around 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.
http://www.cincinnatichildrens.org/svc/alpha/g/gps/default.htm

Significant Publications in FY08

Rogers CC, Alloway RR, Alexander JW, Cardi M, Trofe J, Vinks AA. Pharmacokinetics of mycophenolic acid, tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients: a pilot study. Clin Transplant 2008;22(3):281-91.

Changes in gastro-intestinal anatomy such as after gastric bypass surgery can have profound effects on the absorbtion characteristics of drugs. This is the first pharmacokinetic study of immunosuppressive drugs in obese transplant patients before and after bariatric surgery. Our results show large differences in pharmacokinetics after bypass surgery indicating that transplant recipients with bariatric surgery would need higher doses of tacrolimus, sirolimus and MMF to provide similar exposure to a non-bypass patient.

Aman MG, Vinks AA, Remmerie B, Mannaert E, Ramadan Y, Masty J, et al. Plasma pharmacokinetic characteristics of risperidone and their relationship to saliva concentrations in children with psychiatric or neurodevelopmental disorders. Clin Ther 2007;29(7):1476-86.

Risperidone has not been studied extensively in children and dosing is often by trial and error. This is the first study on the pharmacokinetics and pharmacogenetics of risperidone in pediatric patients with psychiatric and neurodevelopmental disorders, including autism. The results show clinically important differences in drug exposure between patients and provide preminary insight in the genotype-phenotype relationship of risperidone in this patient population. The results provide a basis for ongoing studies in the division conducted by Dr. Saldaña.

Division Highlights

Shannon N. Saldaña, PharmD, MS

Dr. Saldaña was awarded a translational research initiative (TRI) grant to study 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 pharmacogenetics of inosine monophosphate dehydrogenase (IMPDH), a key enzyme in lymphocyte proliferation and drug target for mycophenolate-mofetil immunosuppression. Mycophenolate-mofetil (MMF, CellCept®) is an important drug to protect pediatric kidney transplant patients against organ rejection. As the MMF dose does not very well predict clinical effect or toxicity, finding the right dose for each individual patient is a major clinical problem. Pharmacogenetic factors can be used to help predict what the best MMF dose is a patient and how he or she will respond to the therapy. This proposal will study newly discovered genetic factors in pediatric kidney transplant patients.

Division Collaboration

Collaboration with Neurology; Human Genetics

Collaborating Faculty: Tracy A. Glauser, MD; Diego A. Morita, MD; Kejian Zhang, MD, MBA

Genetic Pharmacology Service and development of pharmacogenetically guided dosing algorithms for epilepsy and neuropsychiatric drugs, and warfarin. Therapeutic drug management.

Collaboration with Nephrology and Hypertension

Collaborating Faculty: Jens Goebel, MD; David Hooper, MD

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: Brian D. Weiss, MD; John P. Perentesis, MD

Role as Clinical Pharmacology Core in national Neurofibromatosis Consortium funded through the Department of Defense. Phase-I concentration - controlled clinical trails of sirolimus in patients with neurofibromatosis.

Collaboration with Rheumatology

Collaborating Faculty: Hermine I. Brunner, MD; AnnaCarmella Sagcal, MD

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

with Lupus. Developing algorithms for individualized dosing.

Collaboration with Anesthesiology

Collaborating Faculty: Senthilkumar Sadhasivam, MD

Pharmacogenetic studies of morphine in perioperative pain management. The studies will also explore other important SNPs that might influence pain perception and response to morphine in children.

Collaboration with Critical Care Medicine

Collaborating Faculty: Hector Wong, MD

NIH grant proposal to conduct a pilot study on the pharmacokinetics of zinc. The data will be used for pharmacokinetic/pharmacodynamic modeling and trial simulation 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

Pharmacokinetic study of leveteracetam in neonates. Seizures occur more frequently in the neonatal period than at any other time in life and are associated with high morbidity and mortality. 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

Development of a bioassay for 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.

Mentions in Consumer Media

- Monitoring Mycophenolic Acid in Solid-Organ Transplant Recipients - Does Therapeutic Drug Monitoring Reduce Organ Rejection and Adverse Events? Clinical Laboratory News , Newsletter

Division Publications

1. Delgado SV, Saldana SN, Barzman DH, Coffey B. Response to duloxetine in a depressed, treatment-resistant adolescent female. *J Child Adolesc Psychopharmacol.* 2007; 17: 889-94.
2. Aman MG, Vinks AA, Remmerie B, Mannaert E, Ramadan Y, Masty J, Lindsay RL, Malone K. Plasma pharmacokinetic characteristics of risperidone and their relationship to saliva concentrations in children with psychiatric or neurodevelopmental disorders. *Clin Ther.* 2007; 29: 1476-86.
3. Mouton JW, Punt N, Vinks AA. Concentration-effect relationship of ceftazidime explains why the time above the MIC is 40 percent for a static effect in vivo. *Antimicrob Agents Chemother.* 2007; 51: 3449-51.
4. Mouton JW, Vinks AA. Continuous infusion of beta-lactams. *Curr Opin Crit Care.* 2007; 13: 598-606.
5. Rogers CC, Alloway RR, Alexander JW, Cardi M, Trofe J, Vinks AA. Pharmacokinetics of mycophenolic acid, tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients: a pilot study. *Clin Transplant.* 2008; 22: 281-91.
6. Syed A, Vinks AA, Zakowski J. Trend in therapeutic monitoring of immunosuppressive drugs. *MLO Med Lab Obs.* 2007; 39: 31-2.
7. Vinks AA, van Rossem RN, Mathot RA, Heijerman HG, Mouton JW. Pharmacokinetics of aztreonam in healthy subjects and patients with cystic fibrosis and evaluation of dose-exposure relationships using monte carlo simulation. *Antimicrob Agents Chemother.* 2007; 51: 3049-55.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

Vinks, A

Pediatric Pharmacology Research Unit
National Institutes of Health
U01 HD 037249 — 02/15/04 - 12/31/08 — $206,239 / $1,173,645

Optimizing MMF Therapy in Pediatric Transplant Patients
National Institutes of Health
K24 HD 050387 — 04/13/06 - 03/31/11 — $130,759 / $649,258

Spigarelli, M

A Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Tamiflu
National Institutes of Health (University of Alabama at Birmingham)
N01 AI030025 — 10/01/07 - 07/31/10 — $5,615 / $188,691

Current Year Direct **$342,613**

Industry Contracts

Vinks, A	
Pfizer, Inc.	$ 16,940
Roche Laboratories, Inc.	$ 15,678
Spigarelli, M	
Novartis Pharmaceuticals	$ 16,867
Proctor and Gamble	$ 3,850
Wyeth Pharmaceuticals	$ 11,628
Walson, P	
GlaxoSmithKline	$ 207
Sciele Pharma, Inc.	$ 7,517

Current Year Direct Receipts **$72,687**

Service Collaborations

Vinks, A	
Isotechnika	$ 112,313
UIMA	$ 36,064
UIMA	$ 4,000

Current Year Direct **$152,377**

Total **$567,677**