

Pediatric Pharmacology Research Unit

DIVISION PROFILE

Number of Faculty	1
Number of Joint Appointment Faculty	6
Number of Other Students (full and part-time)	9
Number of Support Personnel	6
Annual Total Grant Support (direct)	\$348,186
Annual Total Service Collaborations	\$28,570
Annual Total Industry Contracts (direct)	\$24,414
Number of Peer Reviewed Publications	2

FACULTY LISTING

Alexander A. Vinks, PharmD, PhD, Professor of Pediatrics, Director PPRU and Laboratory of Applied Pharmacokinetics & Therapeutic Drug Management

FACULTY JOINT APPOINTMENT LISTING

Tracy A. Glauser, MD, Professor of Pediatrics and Neurology, Neurology

Daniel Nebert, MD, Professor of Medicine and Pediatrics, UC, Environmental Health and Center for Environmental Genetics

Shannon Saldaña, PharmD, MS, Psychopharmacology Specialist Genetic Pharmacology Service, PPRU and Pharmacy

Siva Sivaganesan, PhD, Professor of Mathematical Science, UC, Arts and Science, Mathematical Science

Michael G. Spigarelli, MD, PhD, Assistant Professor of Pediatrics and Internal Medicine, Adolescent Medicine

Philip D. Walson, MD, Professor of Pediatrics, Clinical Pharmacology

OVERVIEW

The Pediatric Pharmacology Research Unit (PPRU) at Cincinnati Children's is one of 13 PPRUs established by the National Institute of Child Health and Human Development (NICHD) in response to the need for appropriate drug therapy for pediatric patients. The 13 PPRUs form a network of research centers throughout the United States with a primary focus on federally sponsored pediatric pharmacology studies. The network has access to large all-inclusive pediatric populations, ranging in age from birth through young adulthood, with approximately 200,000 pediatric inpatient admissions and over two million outpatient visits per year.



Sander Vinks

The network's mission is to facilitate and promote age-specific pediatric labeling of new drugs or drugs already on the market to support their safe and effective clinical use in children. In this process, the network strives to foster cooperative research efforts among academia, industry, and health professionals. The Cincinnati PPRU provides a focus for expertise in pharmacokinetic and pharmacogenetic and drug

metabolism studies, population pharmacokinetic and pharmacodynamic modeling, and clinical trials methodology.

The network currently conducts clinical studies in a wide array of therapeutic areas including antivirals, antibiotics, antifungals, anti-inflammatory agents, gastrointestinal drugs, analgesics, anti-diabetic agents, antipyretics, hormone analogues and antagonists, and new psychoactive agents. The PPRU participates in these collaborative efforts through interaction with other clinical and research divisions on the CCHMC campus. Key to our network success in current year was the submission of two investigator-initiated combined pharmacogenetics, pharmacokinetics and biomarker studies.

Our program has taken an active role in the development of pediatric pharmacology training and has a registered Fellowship Program through the American Board of Clinical Pharmacology, Inc. Critical to the implementation of such a training program is the attainment of a critical mass of faculty with expertise in Pediatric Clinical Pharmacology. At the faculty level, the PPRU continues to provide a mentorship role in the research training of junior faculty in pediatric clinical pharmacology and the performance of clinical trials.

The PPRU is located on the Oak Campus as part of the Cincinnati Center for Clinical Research (CCCR). This facility, located 5 minutes from the main campus, also houses the PPRU's Laboratory of Applied Pharmacokinetics and Therapeutic Drug Management (LAP-TDM).

HIGHLIGHTS

The PPRU team continues to fulfill the mission to facilitate and promote pediatric pharmacology studies and investigator initiated and industry sponsored PPRU network studies at CCHMC. Programmatic resources currently include laboratory support (drug level determinations, pharmacokinetic-pharmacodynamic (PK/PD) analysis), time-shared study coordinator support, and PK/PD study design and trial simulation support. During this fiscal year, there were 15 newly approved PPRU network studies. Our site participated in several of these new studies, bringing the total number of active ongoing studies to 9. Our unit is the lead site for 4 of these 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).

Laboratory of Applied Pharmacokinetics and Therapeutic Drug Management

The PPRU laboratory is one of three laboratories working in accordance with Good Laboratory Practice (GLP) guidelines at the Cincinnati Center for Clinical Research (CCCR). The laboratory develops and provides high quality chromatography-based assays for drug monitoring to support pharmacokinetic studies and clinical trials as part of grant applications and on a contract or fee-for service basis. Current available assays include immunosuppressive drugs, protease inhibitors, and neuron-psychiatric drugs (risperidone and metabolites). The laboratory also provides pharmacokinetic and clinical pharmacology consultation.

During the year the PPRU laboratory served as the central laboratory (in tandem with Mayo Medical Laboratories) for 23 sites participating in a Phase-IIb concentration-controlled trial with a novel immunosuppressant drug (ISA-247, Isotechnika, Inc, Edmonton, Alberta, Canada). In addition, an investigator-initiated TRI funded protocol was developed in collaboration with the Division of Nephrology (Dr. Goebel) to prospectively study the pharmacogenetics of mycophenolate-mofetil (CellCept) in pediatric kidney transplant recipients.

Genetic Pharmacology Service

Drs. Saldaña and Vinks were actively involved in the further development and implementation of the Genetic Pharmacology Service (GPS) at our institution. The GPS is a joint effort between the Divisions of Human Genetics (Richard Wenstrup, MD and Cindy Prows, MSN, RN) and Neurology (Tracy Glauser, MD) and the PPRU. Scientific evidence indicates that pharmacogenetic testing for some medications such as neuron-psychiatric drugs may improve patient safety, can reduce the incidence of side effects and/or reduce the time to reach a therapeutic dose. During this year the GPS team has been working on further improvements of the service including implementation of web based software (Computational Medicine Center, John Pestian, PhD) that would allow incorporation of genetic information with the usual considerations of patient age, weight, disease process, use of other medications, health behaviors and environment to help physicians and nurse

practitioners choose and dose medications that best meet the needs of the individual patient. A GPS consult service is provided by faculty members participating in the PPRU.

Mentoring and Support

During the year the PPRU provided mentorship and training to several faculty members and national and international students. This included dose finding, clinical trial design by simulation for an investigator-initiated study entitled 'Pharmacokinetics of Montelukast in Very Low Birth Weight (VLBW) preterm infants' (Suhas Kallapur, MD, Pulmonary Biology), study design and pharmacokinetic support for a pharmacokinetic study of micafungin (Mycamine) as alternate day anti-fungal prophylaxis in immunocompromised pediatric patients (Parinda Mehta, MD, Hematology/Oncology), and modeling of anti-epileptic drugs pharmacokinetics using a Bayesian approach as part of an NINDS puberty study (Diego Morita, MD, Child Neurology). Ongoing teaching activities included UC's Master program in Clinical Drug Development and capstone projects, a bi-monthly seminar series, and a journal club in collaboration with the Division of Clinical Pharmacology. General themes included "Pharmacogenetics," "Population pharmacokinetic and pharmacodynamic (PK-PD) modeling," and "Therapeutic Drug Monitoring" and dose individualization of medications such as neuro-psychiatric and immunosuppressive drugs.

TRAINING

Kristin Carlsson, PhD		University of Oslo, Norway
Fang Li, PhD Candidate		College of Pharmacy, University of Cincinnati
Marie Malgaz, MS		University of Groningen, The Netherlands
Marjolein Moes, MS		University of Groningen, The Netherlands
Bankole Osuntokun, MD	PL-IV	Fellow Gastroenterology
Maurits de Rotte, MS		University of Groningen, The Netherlands
Reuven Schore, MD	PL-IV	Fellow Hematology/Oncology
Rebecca S. Turner, MS, CCRP		Hematology/Oncology
Zuoqiao Wang, MS		Department of Mathematical Sciences, University of Cincinnati

GRANTS, CONTRACTS AND INDUSTRY AGREEMENTS

Grant and Contract Awards	Annual Direct/Project Period Direct
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Vinks, A		
CCHMC Pediatric Clinical Pharmacology Research Unit		
National Institutes of Health		
U10 HD 037249	02/15/04 – 12/31/08	\$222,498/\$1,173,645
Optimizing MMF Therapy in Pediatric Transplant Patients		
National Institutes of Health		
K24 HD 050387	04/13/06 – 03/31/11	\$125,688/\$649,258
Current Year Direct		\$348,186

Service Collaborations

Vinks, A		
Isotechnika	01/05/06 – 01/04/07	\$28,570/\$221,930
Current Year Direct		\$28,570

Industry Contracts

Vinks, A Roche		\$24,414
	Current Year Direct Receipts	\$24,414
	TOTAL	\$401,170

PUBLICATIONS

1. Jiang Z, Dragin N, Jorge-Nebert LF, Martin MV, Saldaña SN, Vinks AA, Guengerich FP, Aklillu E, Ingelman-Sundberg M, Hammons GJ, Lyn-Cook BD, Kadlubar FF, Saldana SN, Sorter M, Nassr N, von Richter O, Jin L, Nebert DW. Search for an association between the human CYP1A2 genotype and CYP1A2 metabolic phenotype. *Pharmacogenet Genomics* 2006;16(5):359-67.
2. Mehta P, Vinks A, Filipovich A, Vaughn G, Fearing D, Sper C, Davies S. High-dose weekly AmBisome antifungal prophylaxis in pediatric patients undergoing hematopoietic stem cell transplantation: a pharmacokinetic study. *Biol Blood Marrow Transplant* 2006;12(2):235-40.
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