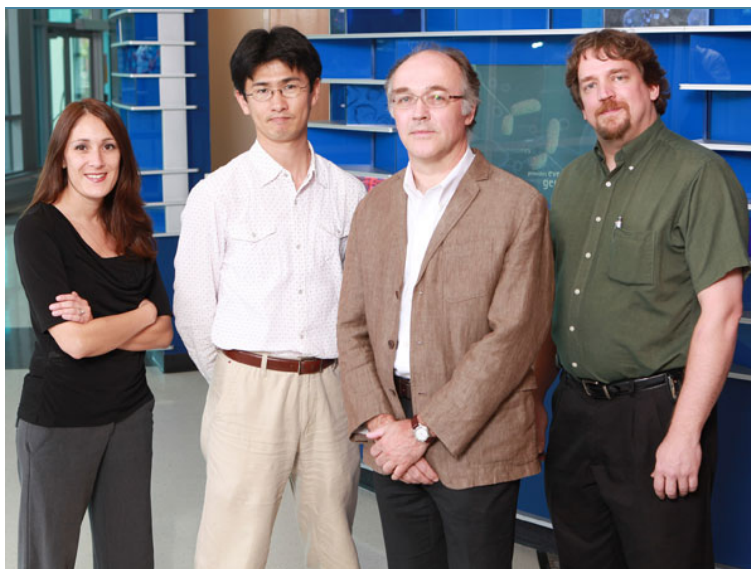


Division Photo



S. Saldana, T. Fukuda, A. Vinks, M. Spigarelli

Division Data Summary

Research and Training Details

Number of Faculty	3
Number of Joint Appointment Faculty	4
Number of Research Fellows	1
Number of Research Students	2
Number of Support Personnel	3
Direct Annual Grant Support	\$335,684
Peer Reviewed Publications	8

Clinical Activities and Training

Number of Clinical Fellows	3
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Significant Publications

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. Apr 23, 2010. Epub ahead of print.

This study describes the prospective evaluation of a sensitive biomarker (IMPDH) of mycophenolic acid (MPA)-induced immunosuppression that can be used for individualized dosing. The results suggest the importance of early drug concentration and biomarker monitoring to improve drug exposure and clinical outcomes. As IMPDH inhibition is well correlated to MPA concentration, pre-transplant IMPDH activity may serve as an early biomarker to guide the initial level of MPA exposure required for optimal therapeutic response in pediatric kidney transplant patients.

Mouksassi MS, Marier JF, Cyran J, Vinks AA. Clinical trial simulations in pediatric patients using realistic covariates: application to teduglutide, a glucagon-like peptide-2 analog in neonates and infants with short-bowel syndrome. Clin Pharmacol Ther. 2009 Dec;86 (6):667-71.

This article describes the application of novel pharmacokinetic-pharmacodynamic (PK/PD) modeling and clinical trial simulation techniques for the design of a Phase-I study in neonates to determine the safety, efficacy, and pharmacokinetics of teduglutide in patients with short-bowel syndrome who have undergone resection for necrotizing enterocolitis, malrotation, or intestinal atresia. The results provided an important example of the application of innovative pharmacometrics techniques to generate age appropriate dosing strategies that have high likelihood of achieving target exposure and therapeutic effect in this patient population.

Division Highlights

Tsuyoshi Fukuda, Ph.D.

Dr. Fukuda was invited for oral and poster presentations 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). His work was presented at the Annual meeting of the American Society of Clinical Pharmacology and Therapeutics (Atlanta, March 2010) and the Japan-Korea Joint Meeting on Clinical Pharmacology (Yokohama, Japan, December 2009).

Shannon N. Saldaña, Pharm.D., M.S.

Dr. Saldaña received a T1 Translational Research Award through the University of Cincinnati Center for Clinical and Translational Science for a study warfarin pharmacogenetics. The goal is to develop a pediatric warfarin dosing algorithm that incorporates clinical information and CYP2C9 and VKORC1 genotypes. In addition she received funding from the Clinical Research Feasibility Funds Program (CREFF) for her ongoing pharmacogenetic studies in risperidone-treated children and adolescents with psychiatric or neurodevelopmental 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.

Michael G. Spigarelli, MD, PhD

Dr. Spigarelli became chair of the Special Population Section of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) and serves 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.

Alexander A. Vinks, Pharm.D., Ph.D.

Dr. Vinks became 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 South America, China and India. As principal investigator of TEENS-LAB ancillary pharmacokinetic, pharmacodynamic and pharmacogenetics study of propofol in morbidly obese patients he and a clinical pharmacology-anesthesia team successfully finalized enrollment. The study 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.

Division Collaboration

Collaboration with Neurology; Human Genetics; Biomedical Informatics

Collaborating Faculty: Tracy A. 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.

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 Behavioral Medicine and Clinical Psychology

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

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

Collaboration with Hematology/Oncology

Collaborating Faculty: John P. Perentesis, MD; Brian D. Weiss, MD; Denise Adams, 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.

Collaboration with Hematology/Oncology

Collaborating Faculty: Nancy Ratner, PhD; Timothy P. Cripe, MD, PhD

Clinical Pharmacology Core in national Neurofibromatosis Consortium.

Collaboration with Anesthesiology

Collaborating Faculty: Senthilkumar Sdahasivam, MD, MPH; Vidya Chidambaran, 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.

Collaboration with Surgery

Collaborating Faculty: Thomas H. Inge, MD, PhD

TEENS-LAB ancillary study to develop of a PK/PD model for propofol dose optimization in bariatric surgery patients.

Collaboration with Critical Care Medicine

Collaborating Faculty: Hector R. Wong, MD; Jennifer Kaplan, MD

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

Collaboration with Neonatology

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

Collaboration with Health Policy and Clinical Effectiveness

Collaborating Faculty: Carole Lannon, MD

Strategies for implementation of pharmacogenetic testing as part of Centers for Education in Research and Therapeutics (CERT) research projects.

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, Assistant Professor

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, Associate Professor

Adolescent Medicine

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

Pediatric Pharmacology Research Unit

The Pediatric Pharmacology Research Unit (PPRU) is one of just 13 units nationwide established by the National Institute of Child Health and Human Development (www.ppru.org). Our mission is to conduct state-of-the-art Phase I - III clinical studies in a safe, effective and timely fashion to enable optimal use of medications in newborns, children and adolescents. Our faculty is particularly interested in pharmacogenetics, and population pharmacokinetic-pharmacodynamic modeling, and has extensive expertise in clinical trial design and simulation. We have ongoing studies in the pharmacogenetics of warfarin, risperidone, and mycophenolic acid (MMF, CellCept®) in transplant patients (with Nephrology). We have a pharmacokinetics-pharmacodynamics study involving children with lupus (with Rheumatology). We also are conducting dose optimization studies (with Anesthesia and Surgery) for the use of propofol in morbidly obese patients.

Immune suppressing therapies

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 NIH 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 (MMF, CellCept®) in pediatric renal transplant recipients and children with Lupus using newly discovered genetic polymorphisms. Our data will help develop dosing algorithms to allow personalized dose tailoring

Genetic pharmacology program

We also work with the Genetic Pharmacology Service, the first of its kind in a pediatric institution. This service focuses on reducing adverse medication effects by identifying genetic variations in drug metabolism, providing dose 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 for neuropsychiatric and anticoagulation drug therapy. Our research focuses on genotyping-phenotyping studies of neuropsychiatric drugs such as risperidone and warfarin and developing computerized decision support systems that integrate evidence based medicine, patient genotypes and phenotypes, as well as advanced drug pharmacology and environmental factors.

Division Publications

1. :

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct / Project Period Direct

Saldana, S

Pediatric Warfarin Dosing Using Genetic & Clinical Data

University of Cincinnati

09/01/09 - 06/30/10

\$100,000 / \$100,000

Vinks, A

Optimizing MNF Therapy in Pediatric Transplant Patients

National Institutes of Health

K24 HD 050387

04/13/06 - 03/31/11

\$134,700 / \$649,258

CCHMC Pediatric Pharmacology Research Unit

National Institutes of Health

U10 HD 037249

01/01/09 - 12/31/10

\$100,984 / \$100,984

Current Year Direct

\$335,684

Current Year Direct Receipts

0

Current Year Direct

0

Funded Collaborative Efforts

Vinks, A

Promoting Treatment Adherence in Adolescent Leukemia

National Institutes of Health

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

5 %

Cincinnati Center of Neurofibromatosis Research

National Institutes of Health

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

6 %

Neurofibromatosis Consortium: Sirolimus Treatment of Plexiform Neurofibromatosis (STOPN)

Department of Defense

Schorry 07/01/08 - 06/30/10

6 %

A Phase II Study of the mTOR Inhibitor Rapamycin for Complicated Vascular Anomalies

National Institutes of Health

Adams 09/22/09 - 07/31/13

5 %

Spigarelli, M

Cincinnati Center for Clinical and Translational Sciences and Training

National Institutes of Health

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

10 %

Total \$ 335,684
