2013 Research Annual Report

Clinical Pharmacology

Cincinnati Children's

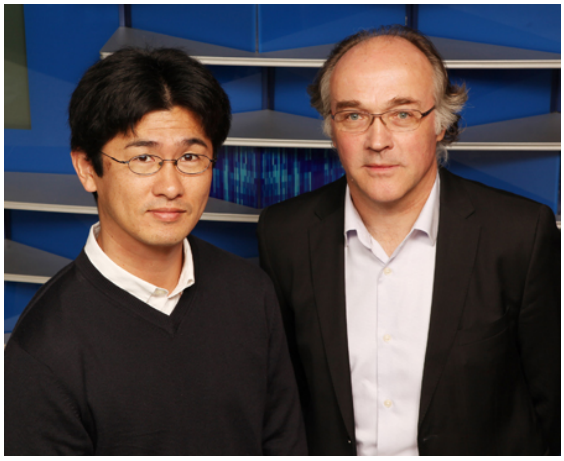
Division Details

Division Data Summary

RESEARCH AND TRAINING DETAILS	
Number of Faculty	2
Number of Joint Appointment Faculty	3
Number of Research Fellows	6
Number of Research Students	3
Number of Support Personnel	3
Direct Annual Grant Support	$213,493
Direct Annual Industry Support	$60,756
Peer Reviewed Publications	23

CLINICAL ACTIVITIES AND TRAINING	
Number of Clinical Staff	1
Number of Clinical Fellows	4

Division Photo



T Fukuda, S Vinks

Significant Accomplishments

Personalized Therapeutics through Pharmacokinetics and Pharmacogenomics

Our research seeks to identify pharmacokinetic (PK), pharmacodynamic (PD) and pharmacogenetic (PGx) factors to explain differences in clinical response to drugs and adverse events in pediatric patients. One important focus area is immunomodulating therapies in transplantation and rheumatology. For decades clinicians have struggled with individualized dosing of drugs to improve clinical outcomes and reduce toxic side effects. With funding from a Place Outcome Award by The James M. Anderson Center for Health Systems Excellence, we worked with David Hooper, MD, and members of Nephrology, Biomedical Informatics, and the Adherence Center and developed a web-based therapeutic decision support system (dashboard) with a graphical user interface. The dashboard is linked to the electronic health record and provides real-time views of individual patient data that are essential for the management of therapy and will alert providers of increased risk of toxicity and drug interaction potential. The novel dashboard includes pharmacokinetic summaries of all immunosuppressive drugs and real-time adherence data and is made available to providers to enhance their medication management decision making. We also continue to participate in the Genetic Pharmacology Service, the first of its kind in a pediatric institution, expanding our pharmacogenetics panels and services for neuropsychiatric drugs, codeine and warfarin.

Pharmacometrics and Systems Pharmacology

As part of the personalized pain initiative, we work with 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. A successful joint effort includes a

study on the disposition of morphine and metabolites that identified important PGx factors in postsurgical patients that could help predict morphine's dose. This finding and its potential role in personalizing analgesia is currently being investigated in a larger cohort of patients. A joint effort with the Center for Bariatric Research and Innovation funded through the translational research initiative was the successful completion of a PK study of propofol in obese patients undergoing bariatric surgery and the development of an evidence based dosing algorithm. With the Cancer and Blood Diseases Institute, we completed a PK-guided study of sirolimus in children with NF1 and plexiform neurofibromas. published. As part of the project we have initiated an *in-vitro/in-vivo* correlation program studying the genetics and developmental aspects of sirolimus disposition. We have identified important differences in metabolic pathways in young patients, a finding that directly benefits the individualized dosing of patients with complicated vascular anomalies who participate in a sirolimus safety and efficacy study funded by the FDA.

T32 Program in Pediatric Clinical Pharmacology

We are one of three sites awarded a pediatric clinical and developmental pharmacology training grant (T32) from the National Institute of Health. This postdoctoral program trains 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 our fellows related to the application of pharmacokinetics and pharmacogenetics/genomics to individualized therapy. Current fellows were selected from a pool of high quality pediatric subspecialty trainee candidates: Dawn Pinchasik, MD, is a third year fellow in Pediatric Hematology-Oncology and our first 2013 graduate. Jason Wiles, MD, is a Neonatology fellow, and Andrea Hahn, MD and Kevin Downes, MD, are Infectious Diseases fellows.

Research 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 investigating the pharmacokinetics (PK) and pharmacogenetics (PG) of sirolimus in patients with neurofibromatosis and vascular anomalies, the PK/PD and PG of mycophenolic acid (MMF, CellCept®) in transplant patients (with Nephrology), and in children with Lupus (with Rheumatology), propofol PK/PG dose optimization studies in morbidly obese patients, and personalized pain treatment with codeine and morphine (with Anesthesia and Surgery).

Alexander A. Vinks, PharmD, PhD

Supported by a Place Outcome Award by The James M. Anderson Center for Health Systems Excellence, Dr. Vinks and his collaborators in Nephrology, Biomedical Informatics and the Adherence Center, developed an electronic health record linked web-based therapeutic decision support platform ('dashboard'). The dashboard provides real time views of individual patient data that are essential for the management of immunosuppressive drug therapy in transplantation and will alert providers of increased risk of toxicity and drug interaction potential.

Dr. Vinks was nominated as the incoming chair of the Clinical Pharmacology and Translational Research Section of the American Association of Pharmaceutical Scientists (AAPS).

Tsuyoshi Fukuda, PhD

Dr. Fukuda has been instrumental in the recruitment of talented post-doctoral fellows from Japan. His team provides pivotal support for the ongoing pharmacokinetic-pharmacogenetics studies of mycophenolate in transplantation and childhood-onset Systemic Lupus Erythematosus (cSLE), 6-mercaptopurine, tacrolimus, most recently morphine, voriconazole, β-lactam, and mTOR inhibitors. His work was selected for presentation at the Annual meeting of the American Society of Clinical Pharmacology and Therapeutics, Indianapolis, Indiana and at the International Congress of Therapeutic Drug Monitoring & Clinical Toxicology, in Salt Lake City, Utah. He was nominated as a committee member of the International Relationship Section of the Japanese Society of Clinical Pharmacology. He continues to lead at our site the National Institute of Health Principles of Clinical Pharmacology Course for our clinical and postdoctoral fellows.

Significant Publications

Diepstraten, J., et al. **Propofol clearance in morbidly obese children and adolescents: influence of age and body size**. *Clin Pharmacokinet*. 2012. 51(8): 543-551.

Given the alarming increase in obesity among children undergoing surgery, the main aim of this study was to characterize propofol clearance in a cohort of morbidly obese children and adolescents in relation to their age and body weight characteristics. A prospective pharmacokinetic study in morbidly obese children and adolescents undergoing elective surgery was conducted.

Twenty obese and morbidly obese children and adolescents (mean age 16 years (range 9-18 years); total body weight (TBW) 125 kg (range 70-184 kg)) were studied. TBW proved to be the most significant determinant for propofol elimination. It is concluded that the propofol dose for maintenance of anesthesia in morbidly obese children and adolescents should be based on TBW using an allometric function.

Fukuda, T., et al.**UGT1A9, UGT2B7, and MRP2 genotypes can predict mycophenolic acid pharmacokinetic variability in pediatric kidney transplant recipients**. *Ther Drug Monit*. 2012. (6): 671-679.

Several genetic variants in glucuronosyltransferases (UGTs) and of multidrug resistance-associated protein 2 (MRP2) have independently been suggested to predict mycophenolic acid pharmacokinetic. We combined contribution of these genetic variants to study MPA pharmacokinetics in pediatric renal transplant recipients. Our results indicate that combined UGT1A9-440C>T, UGT2B7-900A>G, and MRP2-24T>C polymorphisms can be important predictors of interindividual variability in MPA exposure in the pediatric population.

Sadhasivam, S., et al. **Morphine clearance in children: does race or genetics matter?** *J Opioid Manag*. 2012. 8(4): 217-226.

Interindividual variability in analgesic response and adverse effects of opioids because of narrow therapeutic indices are major clinical problems. One hundred forty-six African American and Caucasian children scheduled for elective outpatient adenotonsillectomy were enrolled in our prospective genotype blinded observational study with standard perioperative clinical care. It was observed that African American children have higher morphine clearance than Caucasian children. It was concluded that race of the child is an important factor in perioperative intravenous morphine's clearance and its potential role in personalizing analgesia with morphine needs further investigation.

Scott, J. R., et al. **Population pharmacokinetics of sirolimus in pediatric patients with neurofibromatosis type 1**. *Ther Drug Monit. 2013.* 35(3): 332-337.

The narrow therapeutic index and large between-patient variability in sirolimus pharmacokinetics make therapeutic drug monitoring necessary. Sirolimus concentration-time data were collected from an ongoing prospective trial in children with NF1. Total body weight and body surface area were strong predictors of sirolimus clearance. When normalized for size, an age effect on clearance was observed in the youngest patients, most likely due to maturational changes in drug absorption and metabolism. A mean dose of 2.0 mg/m twice a day was required for attainment of target trough concentrations of 10-15 ng/mL in children older than 3 years of age. The updated model will allow PK-guided individualized dosing of sirolimus in patients with NF1.

Sherwin, C. M., et al. **Population pharmacokinetic modeling of risperidone and 9-hydroxyrisperidone to estimate CYP2D6 subpopulations in children and adolescents**. *Ther Drug Monit.* 2012. 34(5): 535-544.

The study aims were to characterize risperidone and (+/-)-9-hydroxyrisperidone pharmacokinetic (PK) variability in children and adolescents and to evaluate covariate effects on PK parameters. A 1-compartment mixture model described risperidone and (+/-)-9-hydroxyrisperidone clearances for 3 CYP2D6 metabolizer subpopulations: extensive, intermediate, and poor. Weight significantly affected (+/-)-9-hydroxyrisperidone clearance. Active moiety [risperidone plus (+/-)-9-hydroxyrisperidone] PK variability and the covariate effects were better explained with the addition of metabolite PK parameters. This model may aid the development of individualized risperidone dosing regimens in children and adolescents.

Division Publications

1. Abdel-Rahman SM, Amidon GL, Kaul A, Lukacova V, Vinks AA, Knipp GT, Members of the BCSTF. **Summary of the National Institute of Child Health and Human Development-best pharmaceuticals for Children Act Pediatric Formulation Initiatives Workshop-Pediatric Biopharmaceutics Classification System Working Group**. *Clin Ther*. 2012; 34:S11-24.
2. Chidambaran V, Sadhasivam S, Diepstraten J, Esslinger H, Cox S, Schnell BM, Samuels P, Inge T, Vinks AA, Knibbe CA. **Evaluation of propofol anesthesia in morbidly obese children and adolescents**. *BMC Anesthesiol*. 2013; 13:8.
3. Chidambaran V, Venkatasubramanian R, Sadhasivam S, Esslinger HR, Cox SL, Diepstraten J, Fukuda T, Inge TH, Knibbe CA, Vinks AA. **Pharmacokinetic and Pharmacodynamic Modeling of Propofol Depth of Anesthesia in Morbidly Obese Children**. *Clinical Pharmacology & Therapeutics*. 2013; 93:S10-S10.
4. Cohen M, Sadhasivam S, Vinks AA. **Pharmacogenetics in perioperative medicine**. *Curr Opin Anaesthesiol*. 2012; 25:419-27.
5. Diepstraten J, Chidambaran V, Sadhasivam S, Esslinger HR, Cox SL, Inge TH, Knibbe CA, Vinks AA. **Propofol clearance in morbidly obese children and adolescents: influence of age and body size**. *Clin Pharmacokinet*. 2012; 51:543-51.
6. Emoto C, Fukuda T, Cox S, Schniedewind B, Christians U, Vinks AA. **Development of a Physiologically-Based Pharmacokinetics (Pbpk) Model for Serolimus to Explain Inter-Patient Variability**. *Clinical Pharmacology & Therapeutics*. 2013; 93:S40-S41.
7. Emoto C, Yoda N, Uno Y, Iwasaki K, Umehara K, Kashiyama E, Yamazaki H. **Comparison of p450 enzymes between cynomolgus monkeys and humans: p450 identities, protein contents, kinetic parameters, and potential for inhibitory profiles**. *Curr Drug Metab*. 2013; 14:239-52.
8. Fukuda T, Chidambaran V, Mizuno T, Venkatasubramanian R, Ngamprasertwong P, Esslinger HR, Vinks AA, Sadhasivam S. **Organic Cation Transporter 1 Genetic Variants Contribute to Decreased Morphine Clearance in Children.**. *Clinical Pharmacology & Therapeutics*. 2013; 93:S49-S49.

9. Fukuda T, Goebel J, Cox S, Maseck D, Zhang K, Sherbotie JR, Ellis EN, James LP, Ward RM, Vinks AA. **UGT1A9, UGT2B7, and MRP2 genotypes can predict mycophenolic acid pharmacokinetic variability in pediatric kidney transplant recipients**. *Ther Drug Monit*. 2012; 34:671-9.
10. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC, Childhood Absence Epilepsy Study T. **Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months**. *Epilepsia*. 2013; 54:141-55.
11. Hayashi S, Ohashi K, Nakata E, Emoto C. **Discovery of 1-(beta-amino substituted-beta-alanyl)-N,N-dimethylindoline-2-carboxamides as novel nonpeptide antagonists of nociceptin/orphanin FQ receptor: efficient design, synthesis, and structure-activity relationship studies**. *Eur J Med Chem*. 2012; 55:228-42.
12. Mizuno T, Fukuda T, Chidambaran V, Venkatasubramanian R, Niu J, Ngamprasertwong P, Esslinger HR, Vinks AA, Sadhasivam S. **Genotype of Abcc3-211c > T Influences the Pharmacokinetics of Morphine Glucuronide in Children**. *Clinical Pharmacology & Therapeutics*. 2013; 93:S63-S63.
13. Mizuno T, Fukudo M, Terada T, Kamba T, Nakamura E, Ogawa O, Inui K, Katsura T. **Impact of genetic variation in breast cancer resistance protein (BCRP/ABCG2) on sunitinib pharmacokinetics**. *Drug Metab Pharmacokinet*. 2012; 27:631-9.
14. Ngamprasertwong P, Vinks AA, Boat A. **Update in fetal anesthesia for the ex utero intrapartum treatment (EXIT) procedure**. *Int Anesthesiol Clin*. 2012; 50:26-40.
15. Sadhasivam S, Krekels EH, Chidambaran V, Esslinger HR, Ngamprasertwong P, Zhang K, Fukuda T, Vinks AA. **Morphine clearance in children: does race or genetics matter?**. *J Opioid Manag*. 2012; 8:217-26.
16. Scott JR, Courter JD, Saldana SN, Widemann BC, Fisher M, Weiss B, Perentesis J, Vinks AA. **Population pharmacokinetics of sirolimus in pediatric patients with neurofibromatosis type 1**. *Ther Drug Monit*. 2013; 35:332-7.
17. Sherwin CM, Saldana SN, Bies RR, Aman MG, Vinks AA. **Population pharmacokinetic modeling of risperidone and 9-hydroxyrisperidone to estimate CYP2D6 subpopulations in children and adolescents**. *Ther Drug Monit*. 2012; 34:535-44.
18. Shimamoto Y, Fukuda T, Tominari S, Fukumoto K, Ueno K, Dong M, Tanaka K, Shirasaka T, Komori K. **Decreased vancomycin clearance in patients with congestive heart failure**. *Eur J Clin Pharmacol*. 2013; 69:449-57.
19. Teusink A, Vinks A, Zhang KJ, Davies S, Filipovich A, Fukuda T, Nortman S, Kissell D, Dell S, Rhollans L, Mehta P. **Impact of Pharmacogenetics and Therapeutic Drug Monitoring on Optimizing Voriconazole Dosing in Pediatric Patients Undergoing Hematopoieitc Stem Cell Transplantation**. *Pediatric Blood & Cancer*. 2013; 60:S11-S11.
20. Togashi Y, Masago K, Masuda S, Mizuno T, Fukudo M, Ikemi Y, Sakamori Y, Nagai H, Kim YH, Katsura T, Mishima M. **Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer**. *Cancer Chemother Pharmacol*. 2012; 70:399-405.
21. Vinks A. **The Future of Physiologically Based Pharmacokinetic Modeling to Predict Drug Exposure in Pregnant Women**. *CPT: Pharmacometrics & Systems Pharmacology*. 2013; 2:e33.
22. Wiles JR, Vinks AA, Akinbi H. **Federal legislation and the advancement of neonatal drug studies**. *J Pediatr*. 2013; 162:12-5.
23. Yoda N, Emoto C, Date S, Kondo S, Miyake M, Nakazato S, Umehara K, Kashiyama E. **Characterization of intestinal and hepatic P450 enzymes in cynomolgus monkeys with typical substrates and inhibitors for human P450 enzymes**. *Xenobiotica*. 2012; 42:719-30.

Faculty, Staff, and Trainees

Faculty Members

Alexander A. Vinks, PharmD, PhD, Professor

Leadership Division Director; Fellowship Director; Co-Director, Genetic Pharmacology Service; Interim Director, Pharmacy Research in Patient Services

Research Interests Population Pharmacokinetics, Pharmacokinetic- Pharmacodynamic (PK/PD)modeling, Pharmacogenetics/genomics, Clinical Trial Design and Simulation, Pharmacometrics/Systems Pharmacology

Tsuyoshi Fukuda, PhD, Associate Professor

Research Interests Pharmacogenetics, Population PK/PD Modeling, Pharmacometrics/Systems Pharmacology

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, Bayesian statistics

Clinical Staff Members

Shareen Cox, BS,

Senior Research Assistant

Trainees

Min Dong, PhD, 2010, University of Cincinnati
Raja Venkatasubramanian, PhD, 2009, Merck & Company, West Point, PA
Jing Niu, MD, 2007, Wuhan University School of Medicine, Wuhan, PRC
Chie Emoto, PhD, 2006, Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd.
Tomoyuki Mizuno, PhD, 2012, Kyoto University Hospital, Kyoto, Japan
Kana Mizuno, PhD, 2012, Kyoto University, Kyoto, Japan
Andrea Hahn, MD, 2008, Infectious Diseases, Cincinnati Children's Hospital Medical Center
Dawn Pinchasik, MD, 2007, Cancer & Blood Diseases Institute, Cincinnati Children's Hospital Medical Center
Kevin Downes, MD, 2008, Infectious Diseases, Cincinnati Children's Hospital Medical Center
Jason Wiles, MD, 2008, Neonatology, Cincinnati Children's Hospital
Edward Nehus, MD, 2008, Nephrology, Cincinnati Children's Hospital Medical Center
Ralf Stemkens, BS, 2011, University of Utrecht
Thomas Smits, MS, 2010, University of Groningen, the Netherlands
Alison Dixon, PhD student, University of Cincinnati, Cincinnati, Ohio

Division Collaboration

Anesthesiology » Senthilkumar Sadhasivam, MD, MPH, Vidya Chidambaran, MD, and Pornswan Ngamprasertwong, MD

- Population PK/PD and pharmacogenetic studies of morphine in perioperative pain management.
- Propofol and remifentanil in perinatal anesthesia.
- Development of a PK/PD model for propofol dose optimization in obese patients.

Behavioral Medicine & Clinical Psychology » Dennis Drotar, PhD and Ahna Pai, PhD

- Pharmacokinetics and pharmacogenetics of 6-mercaptopurine (6-MP) and metabolites in Acute Lymphoblastic Leukemia (ALL) as a marker for treatment adherence.
- Improving Safety and Efficacy of Mycophenolate Therapy – Development of a web-based therapeutic decision support system for adherence monitoring

Cancer & Blood Diseases Institute » John Perentesis, MD, Brian Weiss, MD, Maryam Fouladi, MD, Denise Adams, MD, Parinda Mehta, MD, Dawn Pinchasik, MD, Maureen O'Brien, MD, and Sonate Jodele, 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.
- 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.
- Predictors of delayed Methotrexate Clearance During High-Dose Therapy.
- Eculizumab therapy in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy

Critical Care Medicine » Jennifer Kaplan, MD and Hector Wong, MD

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

Endocrinology » David Klein, MD

- Risk Factors and Effective Treatments for the Metabolic and Anthropometric Consequences of Antipsychotic Therapy in Pediatric Psychiatry Patients

Heart Institute » David Cooper, MD, MPH and James Cnota, MD

- Evaluation of the Pharmacokinetics of Recombinant Antithrombine-3 in Neonates and Infants Undergoing cardiopulmonary bypass and extracorporeal membrane oxygenation support.
- A Phase I, Dose Escalation Trial of Udenafil in Adolescents with Single Ventricle Physiology After Fontan Palliation (Pediatric Heart Network)

Infectious Diseases » Margaret Hostetter, MD, Andrea Hahn, MD, and Kevin Downs, MD

- Pharmacogenomics of β-lactam Associated Neutropenia.
- Biomarkers for Acute Kidney Injury in patients with Cystic Fibrosis.
- Vancomycin Exposure and Clinical Outcomes in Pediatric Patients with MRSA Infection.

Neonatology » Henry Akinbi, MD and Jason Wiles, MD

- Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome.

Nephrology; Acute Care Nephrology » Jens Goebel, MD, David Hooper, MD, Stuart Goldstein, MD, and Edward

Nehus, MD

- Pharmacogenetics of Mycophenolate to predict Adverse Drug Reactions
- Improving Safety and Efficacy of Mycophenolate Therapy – Development of a web-based therapeutic decision support system ('dashboard').
- Pharmacokinetics of meropenem, milrinone and fentanyl in critically ill patients during continuous renal replacement therapy (CRRT).
- PK/PD modeling and target attainment of meropenem during renal replacement therapy.

Neurology; Human Genetics; Biomedical Informatics » Tracy Glauser, MD, Cynthia Prows, MSN, Kejian Zhang, MD, and John Pestian, PhD

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

Rheumatology » Hermine Brunner, MD, MS and John B. Harley, MD, PhD

- Pharmacokinetic, pharmacogenetics and biomarker studies of mycophenolate and corticosteroids in patients with childhood onset Lupus.
- Developing pediatric pharmacogenetics/genomics applications in the Electronic Medical Records and Genomics (eMERGE) Network.

Surgery » Thomas H. Inge, MD, PhD

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

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct
VINKS, A		
Cincinnati Training Program in Pediatric Clinical and Developmental Pharmacology		
National Institutes of Health		
T32 HD 069054	05/16/11-04/30/16	$179,153
Pharmacokinetic Studies of Tacrollmos in Transplant Patients		
Food & Drug Administration(University of Cincinnati)		
U01 FD 004573	09/15/12-09/14/15	$31,376
Pilot Trial of Bumetanide for Neonatal Seizures		
National Institutes of Health(Children's Hospital Boston)		
R01 NS 066929	08/02/10-06/30/13	$2,964
	Current Year Direct	**$213,493**

Industry Contracts	
VINKS, A	
Pharmaceutical Project Solutions, Inc	$43,032

Arkansas Center for Birth Defects Research	$6,400
London Health Sciences Centre	$6,324
Horizon Pharma USA, Inc	$4,500
Procter and Gamble	$500
Current Year Direct Receipts	**$60,756**
Total	**$274,249**