

2014 Research Annual Report

Clinical Pharmacology



Division Summary

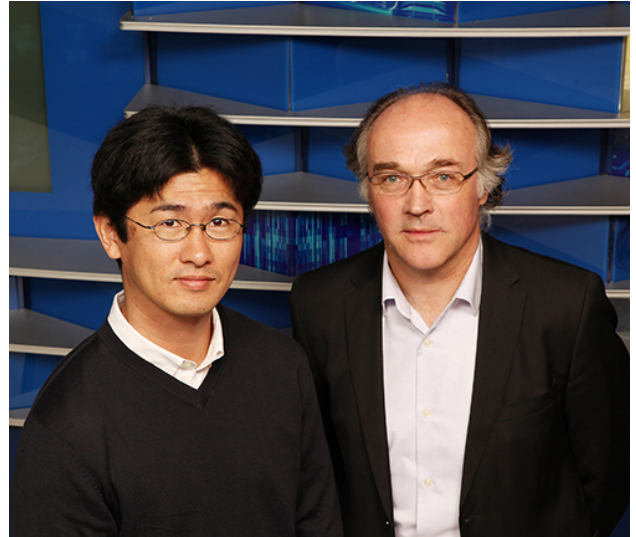
RESEARCH AND TRAINING DETAILS

Number of Faculty	3
Number of Joint Appointment Faculty	3
Number of Research Fellows	5
Number of Support Personnel	2
Direct Annual Grant Support	\$335,282
Peer Reviewed Publications	23

CLINICAL ACTIVITIES AND TRAINING

Number of Clinical Fellows	5
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Division Photo



T Fukuda, S Vinks

Significant Accomplishments

New pharmacogenetic marker to predict morphine pharmacokinetics

Tsuyoshi Fukuda, PhD, discovered novel pharmacogenetic polymorphisms in the Organic Cation Transporter (OCT1), one of the transporters involved in the pharmacokinetics of morphine. Relatively high allelic frequencies of defective OCT1 variants can explain why Caucasian children are slower to eliminate morphine from the body and experience higher rates of adverse events compared to African-American children. Fukuda's paper, published in July 2013 in *Pharmacogenomics*, also was selected as the journal's scientific paper of the month. The study also has led to a CCTST translational research award to explore individualized morphine treatment in neonates. The study will be led by a multidisciplinary team including **Joshua Euteneuer, MD**, a Neonatology fellow who participates in the pediatric clinical pharmacology training program.

Pharmacometrics Program Revolutionizing How We Perform Drug Studies In Children

Our new Pharmacometrics Services Program provides special expertise that can improve pediatric drug development and enhance the success rate of pediatric drug studies. We provide consultation as part of several clinical trials, including studies evaluating sirolimus as a treatment for children with vascular anomalies, leukemia and lymphoma, and optimizing doses of melphalan in bone marrow transplantation. Our research explores the developmental characteristics and genetic polymorphisms of drug metabolizing enzymes and receptors. Among these projects, Chie Emoto, PhD, leads a study that focuses on developing a pharmacokinetic model for sirolimus.

First Clinical Fellows To Graduate From Pediatric Pharmacology Training Program

We are one of three sites in the US awarded a pediatric clinical and developmental pharmacology training grant from the National Institute of Child Health and Development. This postdoctoral program trains clinical

investigators to assume leadership roles in evaluating pediatric therapeutics. Many medicines have not been studied for use in children and few medicines have been developed specifically to treat childhood diseases. One of our major goals is to support and train fellows in applying pharmacokinetics and pharmacogenetics/genomics to individualized therapy. This year's graduates were: Dawn Pinchasik, MD, Jason Wiles, MD, and Andrea Hahn, MD.

Research Highlights

Biomedical Informatics

The University of Cincinnati (UC) and Cincinnati Children's Hospital Medical Center have jointly recruited Peter White to Chair the new Department of Biomedical Informatics. He is actively integrating programs at UC and Cincinnati Children's, implementing a PhD graduate program in biomedical informatics, recruiting additional faculty, and expanding informatics services that support Center for Clinical and Translational Science and Training (CCTST) programs.

UCHealth, the health care delivery system for adults affiliated with the University, has implemented the Epic electronic health record and is working closely with the Center for Health Informatics to expand a research patient data warehouse to support translational research, under the direction of the new Department. This warehouse is closely modeled after, and will complement, the research patient data warehouse at Cincinnati Children's, so our CCTST will now provide translational researchers with integrated information derived from both the adult and pediatric populations. We also have developed a UC I2B2 interface tool that allows researchers to access de-identified data for research planning purposes and dovetails with the existing Cincinnati Children's reporting capacity. As a part of our continuous improvement process, we continue to refine Research Central, our portal for investigators to obtain services from CCTST, with enhanced tracking and integrated services. There has been robust usage of REDCap at both UC and Cincinnati Children's, including surveys and database development.

Biostatistics, Epidemiology & Research Design (BERD)

Research Central, our web portal of entry to CCTST resources, has become a national model as an electronic research record. Its use at UC and Cincinnati Children's has continued to increase. During FY14, Research Central supported 457 projects, including 181 requests for BERD methodological support and 212 for REDCap database/survey development. About 50% of this activity was in support of research at Cincinnati Children's. We are developing a strategy to make this successful program more responsive to the needs of trainees and faculty with varying experience. We are also supporting the growth of a community of methodologists that includes colleagues across the Academic Health Center (AHC), UC and beyond. During FY14, BERD held a series of 14 methodological seminars highlighting work done by local scholars as well as by national experts in biostatistics and epidemiology. In addition, we awarded six pilot grants related to clinical research ethics and biostatistical or study design methodology. BERD has maintained an active role in the network of BERD units affiliated with academic health centers that receive Clinical and Translational Science Awards (CTSAs) from the NIH, and in FY14 we provided logistical and analytic support for the national survey of BERD units, a unique resource of information about the growing number of groups of methodologists who support clinical and translational research. The CCTST Integration Committee of core directors, methodologists and informaticians continues to meet regularly with investigators to recommend strategic direction, identify barriers and help form multidisciplinary teams, while providing ongoing follow-up and support.

Research Education, Training and Career Development

Since its inception, the MS in Clinical and Translational Research Program has experienced a 10-fold increase

in enrollment. The MS in Clinical and Translational Research now has 49 students and 112 alumni, and there are 72 students enrolled in the Certificate in Clinical and Translational Research program with 54 graduates. We have implemented an online curriculum for the Certificate program. We have helped develop and disseminate a Fellows Core Curriculum to Cincinnati Children's and UC residents and fellows. The CCTST runs several career development programs currently, there are three KL2, two CT2, three Building Interdisciplinary Research Careers in Women's Health (BIRCWH) K12 Scholars, and two WH2 Women's Health Scholars in programs administered by the CCTST. The K Club of current and potential career development grant awardees meets monthly, addressing a wide range of topics and promoting peer-to-peer interactions; within the K Club, we have formed a small peer group comprising the KL2, BIRCWH K12, CT2, WH2, and Cincinnati Children's PS2 Scholars. The CCTST continues to support a number of pipeline programs for high school, undergraduate and graduate programs in medicine and pharmacy. The CCTST also conducts mentor training workshops.

Participant and Clinical Interactions Resources (PCIR)

The two sites for the Clinical Translational Research Center (CTRC) at Cincinnati Children's and the VAMC continue to have robust utilization, with increased complexity of visits at each site and increased diversity of users. The nursing staff has been reorganized in the CTRC at Cincinnati Children's, with potential enhanced quality and cost savings. A renewed focus on recruitment and retention is being addressed with efforts directed at coordinating activities across the AHC, taking advantage of a very mature recruitment program at Cincinnati Children's to expand to UC. A CCTST-supported recruitment specialist has been expanding services to UC with considerable success. We have actively participated in ResearchMatch, and have staff supporting retention efforts for studies by using Accruint®, a commercial product designed to find research participants lost to follow-up. The CTRC has transitioned to using the WebCAMP program developed originally for the GCRCs and now used by CTSA organizations to collect study information, census and grant data for the NIH annual reports. The CCTST leadership has been actively involved in the planning and design of the new Cincinnati Children's "Location T" (Clinical Research Services) building, with two floors to be dedicated to outpatient clinical and translational research, scheduled for completion in mid-2015.

Regulatory Knowledge and Support

Regulatory Knowledge and Support is coordinated across the institutions that comprise the AHC through regular meetings and communication. Outreach is a primary focus. In May 2014 we co-sponsored an Office of Human Research Protections (OHRP) regional community forum "Clinical Research and All that Regulatory Jazz" that brought in 450 attendees from the local area and across the country. The annual regional Human Subjects Protection Conference continues to grow and will take place in September. During the last year, the CCTST sponsored other cross-campus symposia for education and debate related to research integrity including the suppression of negative results and pressures to obtain funding, promotions, etc. Online training has been updated and is coordinated across the AHC and local hospitals to facilitate multi-center research. We have also developed and provided templates to facilitate IRB submission and review (e.g. template protocol for medical chart reviews). We have also developed agreements between all but one community hospitals to accept reliance for protocol review for a single IRB. With the other CTSA's in Ohio we continue to build the infrastructure to support a clinical and translational corridor across the state that supports a program called Ohio Clinical Trials Consortium (OCTC).

Community Engagement and Research

The Community Health Grant Program (CHG) awarded more than \$105,000 in grants, leading to at least nine new community-AHC collaborations in diabetes management, childhood asthma, obesity and asthma disparities, obesity prevention and intervention, physical activity in vulnerable populations, access to sexual

healthcare for African American women, substance abuse recovery, bilingual wellness, and tobacco treatment for vulnerable populations. CHG awardees have leveraged more than \$5 million in state and federal funding in the last five years. Within the practice-based research networks (PBRNs), 32 practices have collaborated with the Cincinnati Lifespan Practice Research Consortium to conduct research related to ADHD, asthma, influenza, and community-acquired pneumonia. An AHRQ PBRN COIN grant was awarded to the three CTSA sites in Ohio, one of only eight such grants in the country. The fifth class of 23 graduated from our Community Leaders Institute (CLI), a six-week course to develop leaders in community research and community-based participatory research (CBPR). Trainees from the first four classes have obtained more than \$3 million in grants for their community-based organizations. The CLI has become a national model for training community members and has been replicated at four CTSA sites. The Community Engagement Speaker Series continues to feature prominent national leaders and attract large, diverse audiences, and has also become a national model for promoting bidirectional training. This past year's Speaker Series featured experts on poverty and health and maternal and child health, with the spring series having the highest attendance (N= 323) and satisfaction rating (100% rated very good/excellent) to date. Core training initiatives have resulted in three published manuscripts. Critical to the core's success is the 45-member Community Partner Council (CPC), which meets quarterly and provides input directed at ensuring bidirectional relationships between the community and AHC.

Pilot and Collaborative Translational and Clinical Studies

The PCS core has had six broad-based, campus-wide pilot grant funding cycles. Each cycle attracted applicants from diverse sectors of the AHC and other UC colleges and has supported translational bench-to-bedside (T1) pilot research through Pilot T1 Research Grants, Junior Investigator, and Innovative Core grant awards. In 2013-4, ten Pilot T1 Research Grants, three Junior Investigator Grants, and three Innovative Core Grants were awarded to investigators located at UC or Cincinnati Children's. Similar numbers of awards in each grant category were made in 2014-5. In addition, the PCS Core has continued to provide Just-in-Time (JIT) grant funding of up to \$7,500 to support the use of core laboratory services to help investigators gather additional data for external grant resubmissions or submissions. Twenty-two JIT grants were awarded in 2013-4 and ten have been awarded to date in 2014-5. The PCS Core also continues to provide matching funds (up to \$3,000 per event) to support retreats, workshops, and symposia to foster interactions between clinical, basic, and translational researchers. New in the next year is the Study Section Apprenticeship Program, which is intended to help researchers get a better understanding of the peer-review process and study section dynamics, improve their competitiveness for future grant submissions, and prepare them for active participation in the peer-review process.

Evaluation

The Evaluation Core is a key function area for the CCTST. Core staff attend weekly CCTST staff meetings, participate in all major CCTST functions, and work with other core directors and key CCTST staff to design mechanisms to gather qualitative and quantitative data related to the functioning of CCTST resources and the impact of these services on investigators and institutions. The Evaluation Core maintains the online CCTST Dashboard which includes data on key outcome metrics for each of the CCTST core services. The Core has developed, and maintains, an up-to-date database on publications by CCTST members and member use of various CCTST services. The Evaluation Core also provides consultative services to CCTST cores and members for the development of surveys and other evaluation tools. The Evaluation Core reports provide insight into the impact of the CCTST on research across the partner institutions and are used to develop innovations such as the Integration Committee and Team Science. Many of the resources and strategies developed by the Evaluation Core have become models for other CTSA sites.

Significant Publications

Fukuda T, Chiadambaran V, Mizuno T, Venkatasubramanian R, Ngamprasertwong P, Olbrecht V, Esslinger HR, Vinks AA, Sadhasivam S. **OCT1 genetic variants influence the pharmacokinetics of morphine in children.** *Pharmacogenomics*. 2013 Jul;14(10):1141-51.

Large between patient variability in morphine disposition contributes to unpredictable differences in morphine pain relief and adverse events. In this study we investigated the variations in intravenous morphine pharmacokinetics in children and examined the influence of pharmacogenetic polymorphisms in an important organic cation transporter (OCT1). We found that OCT1 genotypes play a significant role in morphine pharmacokinetics. High allelic frequencies of defective OCT1 variants among Caucasians could explain their lower morphine clearance and higher frequencies of adverse events compared with African-American children. These findings will help in the development of personalized dosing guidelines for morphine.

Emoto C, **Fukuda T**, Cox S, Christians U, **Vinks AA**. **Development of a Physiologically-Based Pharmacokinetic Model for Sirolimus: Predicting Bioavailability Based on Intestinal CYP3A Content.** *CPT: pharmacometrics systems pharmacology*. *CPT Pharmacometrics Syst Pharmacol*. 2013 Jul 24;2:e59.

Sirolimus is an inhibitor of mammalian target of rapamycin (mTOR) and is increasingly being used in pediatric transplantation and cancer therapies. Sirolimus is a low oral bioavailability drug with large pharmacokinetic variability. Sirolimus is extensively metabolized but the relative contribution of the metabolic pathways involved is not known. We studied the metabolic pathways and used the information to develop a physiologically based pharmacokinetic (PBPK) model by describing important mechanism-based factors contributing to observe between patient PK variability. This will facilitate individualized dose adjustments based on therapeutic drug monitoring data.

Mizuno T, **Fukuda T**, Masuda S, Uemoto S, Matsubara K, Inui K, **Vinks AA**. **Developmental trajectory of intestinal MDR1/ABCB1 mRNA expression in children.** *Br J Clin Pharmacol*. 2014 May;77(5):910-2.

Drug transporters play a major role on the distribution and elimination of drugs from the body. There is very little known of the effects of growth and maturation on the activity of drug transporters. This is one of the first studies to document the effect of developmental on P-glycoprotein (MDR1/ABCB1), an important ATP-binding cassette transporter, located in the small intestine that mediates the efflux of many drug from the circulation. These results will help us better understand the influence of growth and maturation on the pharmacokinetics of drugs used in neonates and children.

Roberts JA, Abdjul-Aziz MH, Lipman J, Mouton JW, **Vinks AA**, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL. **Individualized antibiotic dosing for patients who are critically ill: challenges and potential solutions.** *Lancet Infect Dis*. 2014 Jun;14(6):498-509.

Infections in critically ill patients are associated with persistently poor clinical outcomes. These patients have severely altered and variable antibiotic pharmacokinetics and are infected by less susceptible pathogens. Antibiotic dosing that does not account for these features is likely to result in suboptimum outcomes. This report by an international study group from the International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases describes novel computer PK/PD model-based approaches for individualized antibiotic therapy that increases the accuracy of dosing and optimizes care for critically ill patients.

Vinks AA, Derendorf H, Mouton JW. *Fundamentals of antimicrobial pharmacokinetics and pharmacodynamics*. New York, Springer, 2014.

Over the past decade, significant progress has been made in the theory and applications of pharmacodynamics of antimicrobial agents. The study of pharmacokinetic-pharmacodynamic relationships is considerable value in understanding drug action, defining optimal dosing regimens, and in making predictions

under new or changing pre-clinical and clinical circumstances. Not surprisingly, pharmacokinetic-pharmacodynamic modeling concepts are increasingly applied in both research and clinical care as well as in drug development. The book describes the application of pharmacokinetic-pharmacodynamic principles for the optimization of antimicrobial therapy in infectious diseases. The integration of pharmacokinetics with pharmacodynamics for all major classes of antibiotics provide important guidance for personalized treatment in patients.

Division Publications

1. Diepstraten J, Chidambaran V, Sadhasivam S, Blusse van Oud-Alblas HJ, Inge T, van Ramshorst B, van Dongen EP, Vinks AA, Knibbe CA. **An integrated population pharmacokinetic meta-analysis of propofol in morbidly obese and nonobese adults, adolescents, and children.** *CPT Pharmacometrics Syst Pharmacol.* 2013; 2:e73.
2. Dong M, Fukuda T, Vinks AA. **Optimization of mycophenolic acid therapy using clinical pharmacometrics.** *Drug Metab Pharmacokinet.* 2014; 29:4-11.
3. Downes KJ, Hahn A, Wiles J, Courter JD, Vinks AA. **Dose optimisation of antibiotics in children: application of pharmacokinetics/pharmacodynamics in paediatrics.** *Int J Antimicrob Agents.* 2014; 43:223-30.
4. Emoto C, Fukuda T, Cox S, Christians U, Vinks AA. **Development of a Physiologically-Based Pharmacokinetic Model for Sirolimus: Predicting Bioavailability Based on Intestinal CYP3A Content.** *CPT Pharmacometrics Syst Pharmacol.* 2013; 2:e59.
5. Filler G, Vinks AA, Huang SH, Jevnikar A, Muirhead N. **Similar MPA exposure on modified release and regular tacrolimus.** *Ther Drug Monit.* 2014; 36:353-7.
6. Fukuda T, Chidambaran V, Mizuno T, Venkatasubramanian R, Ngamprasertwong P, Olbrecht V, Esslinger HR, Vinks AA, Sadhasivam S. **OCT1 genetic variants influence the pharmacokinetics of morphine in children.** *Pharmacogenomics.* 2013; 14:1141-51.
7. Fukudo M, Ito T, Mizuno T, Shinsako K, Hatano E, Uemoto S, Kamba T, Yamasaki T, Ogawa O, Seno H, Chiba T, Matsubara K. **Exposure-toxicity relationship of sorafenib in Japanese patients with renal cell carcinoma and hepatocellular carcinoma.** *Clin Pharmacokinet.* 2014; 53:185-96.
8. Gottesman O, Kuivaniemi H, Tromp G, Faucett WA, Li R, Manolio TA, Sanderson SC, Kannry J, Zinberg R, Basford MA, Brilliant M, Carey DJ, Chisholm RL, Chute CG, Connolly JJ, Crosslin D, Denny JC, Gallego CJ, Haines JL, Hakonarson H, Harley J, Jarvik GP, Kohane I, Kullo IJ, Larson EB, McCarty C, Ritchie MD, Roden DM, Smith ME, Bottinger EP, Williams MS, et al. **The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future.** *Genet Med.* 2013; 15:761-71.
9. Hahn A, Vinks AA. **Lower vancomycin serum trough concentrations might not be the answer.** *Pediatr Infect Dis J.* 2013; 32:1403-4.
10. Ishii T, Hatano E, Taura K, Mizuno T, Kawai T, Fukudo M, Katsura T, Uemoto S. **Sorafenib in a hepatocellular carcinoma patient with end-stage renal failure: A pharmacokinetic study.** *Hepatol Res.* 2014; 44:685-8.
11. Jodele S, Fukuda T, Vinks A, Mizuno K, Laskin BL, Goebel J, Dixon BP, Teusink A, Pluthero FG, Lu L, Licht C, Davies SM. **Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy.** *Biol Blood Marrow Transplant.* 2014; 20:518-25.
12. Kunitatsu S, Mizuno T, Fukudo M, Katsura T. **Effect of P-glycoprotein and breast cancer resistance protein inhibition on the pharmacokinetics of sunitinib in rats.** *Drug Metab Dispos.* 2013; 41:1592-7.
13. Mizuno T, Fukuda T, Masuda S, Uemoto S, Matsubara K, Inui K, Vinks AA. **Developmental trajectory of intestinal MDR1/ABCB1 mRNA expression in children.** *Br J Clin Pharmacol.* 2014; 77:910-2.

14. Mizuno T, Fukudo M, Fukuda T, Terada T, Dong M, Kamba T, Yamasaki T, Ogawa O, Katsura T, Inui K, Vinks AA, Matsubara K. **The effect of ABCG2 genotype on the population pharmacokinetics of sunitinib in patients with renal cell carcinoma.** *Ther Drug Monit.* 2014; 36:310-6.
15. Pian P, Labovitz E, Hoffman K, Clavijo CF, Rzasa Lynn R, Galinkin JL, Vinks AA, Malik P, Christians U. **Quantification of the 5-lipoxygenase inhibitor zileuton in human plasma using high performance liquid chromatography-tandem mass spectrometry.** *J Chromatogr B Analyt Technol Biomed Life Sci.* 2013; 937:79-83.
16. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL, International Society of Anti-Infective P, the P, Pharmacodynamics Study Group of the European Society of Clinical M, Infectious D. **Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions.** *Lancet Infect Dis.* 2014; 14:498-509.
17. Sagcal-Gironella AC, Fukuda T, Klein-Gitelman MS, Vinks AA, Brunner HI. **A156: pharmacokinetics and pharmacogenetics of mycophenolic Acid and response to therapy in childhood-onset systemic lupus erythematosus.** *Arthritis Rheumatol.* 2014; 66 Suppl 11:S202.
18. Sherwin CM, Ngamprasertwong P, Sadhasivam S, Vinks AA. **Utilization of optimal study design for maternal and fetal sheep propofol pharmacokinetics study: a preliminary study.** *Curr Clin Pharmacol.* 2014; 9:64-9.
19. Shimamoto Y. **Pharmacokinetic implications of augmented renal clearance (ARC) in patients with systemic inflammatory response syndrome (SIRS)/sepsis: Importance of therapeutic drug management (TDM).** *Jpn J Ther Drug Monitoring.* 2014; 31:57-61.
20. Shimamoto Y, Fukuda T, Tanaka K, Komori K, Sadamitsu D. **Systemic inflammatory response syndrome criteria and vancomycin dose requirement in patients with sepsis.** *Intensive Care Med.* 2013; 39:1247-52.
21. Vinks AA, Derendorf H, Mouton JW. **Fundamentals of antimicrobial pharmacokinetics and pharmacodynamics.** New York; Springer.
22. Wang C, Sadhavisvam S, Krekels EH, Dahan A, Tibboel D, Danhof M, Vinks AA, Knibbe CA. **Developmental changes in morphine clearance across the entire paediatric age range are best described by a bodyweight-dependent exponent model.** *Clin Drug Investig.* 2013; 33:523-34.
23. Weiss B, Widemann BC, Wolters P, Dombi E, Vinks AA, Cantor A, Korf B, Perentesis J, Gutmann DH, Schorry E, Packer R, Fisher MJ. **Sirolimus for non-progressive NF1-associated plexiform neurofibromas: an NF clinical trials consortium phase II study.** *Pediatr Blood Cancer.* 2014; 61:982-6.

Faculty, Staff, and Trainees

Faculty Members

Alexander A. Vinks, PharmD, PhD, Professor

Leadership Division Director; Fellowship Director; Co-Director, Genetic Pharmacology Service; Interim Scientific 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

Chie Emoto, PhD, Adjunct

Research Interests In vitro-in vivo extrapolation (IVIVE), physiologically-based pharmacokinetic (PBPK) modeling, and pharmacometrics as it relates to drug pharmacokinetics and pharmacodynamics (PK/PD) in

the pediatric population

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

Senthikumar Sadhasivam, MD, MDH, Associate Professor (Anesthesiology)

Research Interests Pharmacogenetics/genomics, personalized pain management

Siva Sivaganesan, PhD, Professor (Arts & Science, Mathematical Science)

Research Interests Population modeling and simulation, Bayesian statistics

Trainees

- **Min Dong, PhD**, 2010, University of Cincinnati, Cincinnati, Ohio
- **Kevin Downes, MD**, 2008, Infectious Diseases, Cincinnati Children's Hospital Medical Center
- **Joshua Euteneuer, MD**, 2010, Neonatology, Cincinnati Children's Hospital Medical Center
- **Katja Gist, DO**, 2013, Critical Care Medicine, Cincinnati Children's Hospital Medical Center
- **Andrea Hahn, MD**, 2008, Infectious Diseases, Cincinnati Children's Hospital Medical Center
- **Kana Mizuno, PhD**, 2012, Kyoto University, Kyoto, Japan
- **Tomoyuki Mizuno, PhD**, 2012, Kyoto University Hospital, Kyoto, Japan
- **Jing Niu, MD**, 2007, Wuhan University School of Medicine, Wuhan, PRC
- **Raja Venkatasubramanian, PhD**, 2009, Merck & Company, West Point, Pennsylvania
- **Jason Wiles, MD**, 2008, Neonatology, Cincinnati Children's

Division Collaboration

Population PK/PD and pharmacogenetic studies of morphine in perioperative pain management (Min Dong, PhD, Jing Niu, MD, Tomoyuki Mizuno, PhD, Raja Venkatasubramanian, PhD, Sander Vinks, PharmD, PhD, FCP)

Anesthesiology » Vidya Chidambaran MD and Senthil Sadhasivam MD, MPH

Development of a PK/PD model for morphine dose optimization as part of personalized pain management initiative. (Raja Venkatasubramanian, PhD, Sander Vinks, PharmD, PhD, FCP)

Anesthesiology » Senthil Sadhasivam, MD, MPH

Propofol and remifentanyl in perinatal anesthesia (Min Dong, PhD, Raja Venkatasubramanian, PhD, Sander Vinks, PharmD, PhD, FCP)

Anesthesiology » Pornswan Ngamprasertwong MD

Better outcomes for children: GWAS & PHEWAS in eMERGE-II (Sander Vinks, PharmD, PhD, FCP)

Center for Autoimmune Genomics and Etiology » John Harley, MD, PhD

Promoting treatment adherence in adolescent leukemia. Improving Safety and Efficacy of Mycophenolate Therapy. 5R01CA119162 (Tsuyoshi Fukuda PhD, Sander Vinks, PharmD, PhD, FCP)

Behavioral Medicine and Clinical Psychology » Dennis Drotar, PhD and Jennifer Rohan, PhD

Development of a web-based therapeutic decision support system for adherence monitoring (Sander Vinks, PharmD, PhD, FCP)

Behavioral Medicine and Clinical Psychology » Ahna Pai, PhD

Biomedical Informatics » Keith Marsolo, PhD

Nephrology and Hypertension » David Hooper, MD

Patients like Mine cohort retrieval system (Sander Vinks, PharmD, PhD, FCP)

Biomedical Informatics » John Pestian, PhD

Neurology, and Research Administration » Tracy Glauser, MD

Melphalan Pharmacokinetics in Children undergoing Hematopoietic Stem Cell Transplantation: A Pilot Study. Pharmacokinetic data analysis with development of a paper spray assay for bed side monitoring (Kana Mizuno, PhD, Tsuyoshi Fukuda, PhD, Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Bone Marrow Transplantation and Immune Deficiency » Sharat Chandra, MD, Stella Davies MB BS, PhD, MRCP, and Parinda Mehta, MD

Micafungin anti-fungal prophylaxis in immunocompromised pediatric patients: a pharmacokinetic study. Pharmacokinetic data analysis and modeling of optimal dosing regimens (Tsuyoshi Fukuda PhD, Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Bone Marrow Transplantation and Immune Deficiency » Sharat Chandra, MD, Stella Davies MB BS, PhD, MRCP, and Parinda Mehta, MD

Eculizumab therapy in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy. Pharmacokinetic data analysis and development of a Bayesian dosing tool (Tsuyoshi Fukuda, PhD, Kana Mizuno, PhD, Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Bone Marrow Transplantation and Immune Deficiency » Sonata Jodele, MD

Maraviroc as graft versus host disease prophylaxis in pediatric stem cell transplant recipients. Study design support and pharmacokinetic data analysis and modeling. (Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Bone Marrow Transplantation and Immune Deficiency » Stella Davies MB BS, PhD, MRCP and Pooja Khandelwal, MD

Study design support and pharmacokinetic data analysis and modeling 5R01FD004383 - Phase I study of quercetin for the treatment of fanconi anemia. (Tsuyoshi Fukuda, PhD, Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Bone Marrow Transplantation and Immune Deficiency » Parinda Mehta, MD

A Phase I Trial of Zileuton in Sickle Cell Disease. Study design support and pharmacokinetic data analysis and modeling (Min Dong, PhD, Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Hematology » Punam Malik, MD

Identification of novel and interacting pharmacogenetic variants that determine differential sirolimus clearance in

children with neurofibromatosis type 1 and plexiform neurofibromas (Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Oncology » John Perentesis, MD and Jordan Wright, MD
Biomedical Informatics » Bruce Aronow, PhD

Study design support and pharmacokinetic data analysis and modeling. Real-time pharmacokinetically guided dosing recommendations for individualized sirolimus dosing 5R01FD003712 - Phase II study of rapamycin for complicated vascular anomalies (Chie Emoto, PhD, Tsuyoshi Fukuda, PhD, Tomoyuki Mizuno, PhD, Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Oncology » Denise Adams, MD, John Perentesis, MD, FAAP, and Brian Weiss, MD

COG - 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. Pharmacokinetic data analysis and modeling (Kana Mizuno, PhD, Tomoyuki Mizuno, PhD, Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Oncology » Maryam Fouladi, MD, MSc

Pilot study of sirolimus plus multiagent chemotherapy for relapsed/refractory acute lymphoblastic leukemia/lymphoma. Real-time pharmacokinetically guided individualized dosing support (Kana Mizuno, PhD, Tomoyuki Mizuno, PhD, Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Oncology » Maureen O'Brien, MD

Predictors of delayed Methotrexate Clearance During High-Dose Therapy. Pharmacokinetic data modeling and identification of risk parameters for adverse events (Tsuyoshi Fukuda, PhD, Kana Mizuno, PhD, Tomoyuki Mizuno, PhD, Sander Vinks, PharmD, PhD, FCP)

Cancer and Blood Diseases Institute, Oncology » Andrew Bukowinski, MD and Maureen O'Brien, MD

Pharmacokinetic Characteristics of Pioglitazone and Preliminary Biomarker Response in Adolescents Aged 12 to 17 Years with Severe Sepsis and Septic Shock. Study design and pharmacokinetic data analysis and dose finding modeling. (Sander Vinks PharmD, PhD, FCP)

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

Pharmacokinetics of zinc supplementation in critically ill children. Pharmacokinetic data analysis and exposure modeling in support of dose finding (Sander Vinks, PharmD, PhD, FCP)

Critical Care Medicine » Hector Wong, MD

Risk Factors and Effective Treatments for the Metabolic and Anthropometric Consequences of Antipsychotic Therapy in Pediatric Psychiatry Patients. Pharmacogenetic data modeling to predict risk of weight gain (Min Dong, PhD, Sander Vinks, PharmD, PhD, FCP)

Endocrinology » David Klein, MD

Anti-TNF therapy for refractory colitis in hospitalized children (ARCH). PK study design and pharmacokinetic data analysis and exposure modeling for individualized dosing (Min Dong PhD, Sander Vinks, PharmD, PhD, FCP)

Gastroenterology, Hepatology and Nutrition » Lee Denson, MD and Michael Rosen, MD

CYP3A4/5 and Nuclear Factor Gene Mutations Influence Pediatric Heart Transplant Outcomes (Tsuyoshi Fukuda, PhD, Sander Vinks, PharmD, PhD, FCP)

Heart Institute, Cardiology » Chesney Castleberry, MD

Precision medicine of rosuvastatin therapy in children with combined dyslipidemia of obesity - relationship of genetic polymorphisms, individual drug exposure, effect and safety, Pediatric Heart Network (Sander Vinks, PharmD, PhD, FCP)

Heart Institute, Cardiology » James Cnota, MD

Evaluation of the Pharmacokinetics of Recombinant Antithrombin-3 in Neonates and Infants Undergoing cardiopulmonary bypass and extracorporeal membrane oxygenation support (Min Dong, PhD, Sander Vinks, PharmD, PhD, FCP)

Heart Institute, Cardiology » David Cooper, MD, MPH

Genetic Pharmacology Service (Sander Vinks, PharmD, PhD, FCP)

Human Genetics » Cynthia Prows MSN and Kejian Zhang, MD

Neurology, and Research Administration » Tracy Glauser, MD

Vancomycin Exposure and Clinical Outcomes in Pediatric Patients with MRSA Infection (Sander Vinks, PharmD, PhD, FCP)

Infectious Diseases » Andrea Hahn, MD

Pharmacogenomics of β -lactam Associated Neutropenia.(Tsuyoshi Fukuda, PhD, Tomoyuki Mizuno PhD, Sander Vinks, PharmD, PhD, FCP)

Infectious Diseases » Andrea Hahn, MD

Biomarkers for Acute Kidney Injury in patients with Cystic Fibrosis (Sander Vinks, PharmD, PhD, FCP)

Infectious Diseases » Kevin Downes, MD

Nephrology and Hypertension » Stuart Goldstein, MD

Pharmacogenetics of Mycophenolate mofetil (Tsuyoshi Fukuda, PhD)

Nephrology » Jens Goebel, MD and David Hooper, MD

Improving Safety and Efficacy of Mycophenolate Therapy – Prospective evaluation of a web-based therapeutic decision support system ('dashboard') (Sander Vinks, PharmD, PhD, FCP)

Nephrology » Jens Goebel, MD and David Hooper, MD

Pharmacokinetics of meropenem, milrinone and fentanyl in critically ill patients during continuous renal replacement therapy (CRRT) (Sander Vinks, PharmD, PhD, FCP)

Nephrology » Stuart Goldstein MD and Edward Nehus MD

Meropenem in Children Receiving Continuous Renal Replacement Therapy: Clinical Trial Simulations Using Realistic Covariate (Sander Vinks, PharmD, PhD, FCP)

Nephrology and Hypertension » Stuart Goldstein MD and Edward Nehus MD

Population Pharmacokinetic and Pharmacodynamic Analysis of Ethosuximide, Lamotrigine and Valproic Acid in Children with Childhood Absence Epilepsy 5U01NS045911 (Min Dong, PhD, Tsuyoshi Fukuda, PhD, Kana Mizuno, PhD Sander Vinks, PharmD, PhD, FCP)

Neurology, and Research Administration » Tracy Glauser, MD

Cortical Excitability: Phenotype and Biomarker in ADHD - 5R01MH095014 (David Hahn, PhD, Tsuyoshi Fukuda, PhD)

Neurology » Donald Gilbert, MD

University of Cincinnati, Department of Psychiatry & Behavioral Neuroscience » Floyd R. Sallee, MD, PhD

Direct Analysis of Melphalan in Human Whole Blood by Paper Spray Ionization using Mass Spectrometry (Kana Mizuno, PhD, Sander Vinks, PharmD, PhD, FCP)

Pathology and Laboratory Medicine » Ken Setchell, PhD and Junfang Zhao, PhD

Whole Blood Paper Spray assay for Morphine for Individualized Treatment in Neonates (Sander Vinks, PharmD, PhD, FCP)

Pathology and Laboratory Medicine » Ken Setchell, PhD and Junfang Zhao, PhD

Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome (Tomoyuki Mizuno PhD, Sander Vinks, PharmD, PhD, FCP)

Section of Neonatology, Perinatal and Pulmonary Biology » Henry Akinbi, MD and Jason Wiles, MD

Novel pharmacokinetic/pharmacogenetic approach for individualized morphine treatment in neonates. (Tsuyoshi Fukuda, PhD, Sander Vinks, PharmD, PhD, FCP)

Section of Neonatology, Perinatal and Pulmonary Biology » Joshua Euteneuer, MD and Louis Muglia, MD

Novel model-based approach for individualized morphine treatment in neonates (Tsuyoshi Fukuda, PhD, Sander Vinks, PharmD, PhD, FCP)

Section of Neonatology, Perinatal and Pulmonary Biology » Joshua Euteneuer, MD and Louis Muglia, MD

Pathology and Laboratory Medicine » Ken Setchell, PhD

Tacrolimus Pharmacokinetic Modeling Predicts Dose Requirement in Pediatric Heart Transplant Recipients (Tomoyuki Mizuno, PhD, Sander Vinks, PharmD, PhD, FCP)

Clinical Pharmacology » Breann Taylor, PharmD

Heart Institute, Cardiology » Chesney Castleberry, MD

Evaluation of Antithrombotic Therapy and Risk of Thrombosis in Congenital Heart Disease Patients after the Fontan Procedure (Sander Vinks, PharmD, PhD, FCP)

Clinical Pharmacology » Jenna Faircloth, PharmD, BCPS

Heart Institute, Cardiology » Gruschen Veldtman, MD

Pharmacokinetic, pharmacogenetics and biomarker studies of mycophenolate and corticosteroids in patients with childhood onset Lupus (Min Dong, PhD, Tsuyoshi Fukuda, PhD, Sander Vinks, PharmD, PhD, FCP)

Rheumatology » Hermine Brunner, MD

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	\$195,182
Pharmacokinetic Studies of Tacrolimus in Transplant Patients		
Food & Drug Administration(University of Cincinnati)		
U01 FD 004573	09/15/12-09/14/15	\$51,539
Evaluation of Clinical and Safety Outcomes Associated with Conversion from Brand-Name to Generic Tacrolimus Products in High Risk Transplant Recipients		
Food and Drug Administration(University of Cincinnati)		
HHSF223201310224C	09/26/13-09/25/16	\$88,561
Current Year Direct		\$335,282
Total		\$335,282