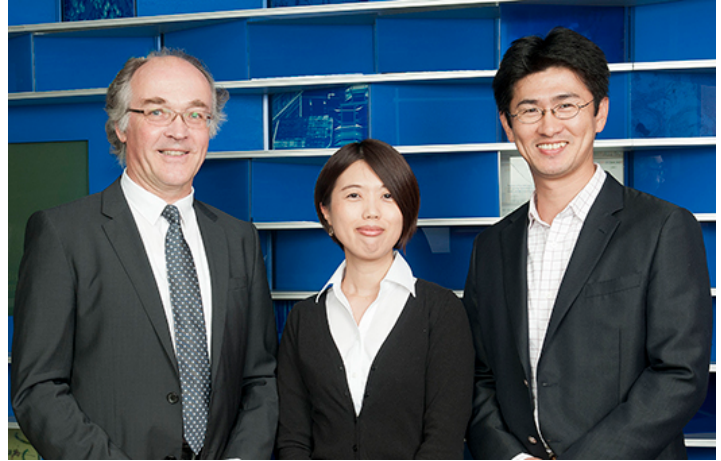


Clinical Pharmacology

RESEARCH AND TRAINING DETAILS



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Faculty	3
Joint Appointment Faculty	3
Research Fellows	6
Research Students	3
Support Personnel	2
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CLINICAL ACTIVITIES AND TRAINING

Clinical Fellows	3
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Research Highlights

Novel Systems Pharmacology Platform for Individualized Morphine Treatment in Neonates

[Tsuyoshi Fukuda, PhD](#), led a CCTST translational research award to explore individualized morphine treatment in neonates. The study involved a multidisciplinary team including [Joshua Euteneuer, MD](#), a neonatology fellow who participates in the [T32 Pediatric Clinical Pharmacology Training Program](#). The study was conducted in parallel with the

Perinatal Institute's Pilot and Feasibility Program grant to develop a rapid bedside test for the measurement of morphine in blood led by [Sander Vinks, PharmD, PhD](#). The goal is to develop a procedure as simple as used for glucose monitoring in diabetes patients: a single drop of blood is analyzed for morphine in real time. The results are uploaded into a web-based application for pharmacokinetically-guided individualized dosing. This will allow clinicians to tailor morphine amount to each neonate's needs at the bedside.

Pharmacometrics Program Revolutionizing How We Perform Drug Studies in Children

Our [Pharmacometrics Services Program](#) continues to provide unique pediatric expertise to improve pediatric drug development and enhance the success rate of drug studies in neonates, infants, children and adolescents. The program provides consultation as part of several clinical trials, including studies evaluating sirolimus as a treatment for children with vascular anomalies, everolimus in patients with tuberous sclerosis, and optimizing dosing of hydroxyurea in children with sickle cell anemia. 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 physiologically-based pharmacokinetic models for morphine, methadone and mTOR inhibitors such as sirolimus.

NIH program to train the next generation of pediatric clinical pharmacologists

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. Our program actively participates in the Adult and Pediatric Clinical Pharmacology Training Network established by the [National Institutes of General Medical Sciences \(NIGMS\)](#) and Child Health and Development (NICHD) as a strategic initiative to increase the pool of pediatric clinical pharmacologists.

Alexander A. Vinks, PharmD, PhD, FCP

[Sander Vinks, PharmD, PhD](#), received an Innovation Fund Award to support and accelerate the development of a novel systems pharmacology platform for individualized morphine treatment in neonates. This cloud-based technology will help clinicians decide how much morphine to give to newborn babies. The platform, which would integrate with electronic health records, would use genetic markers, demographic data, clinical data and lab results to suggest individualized dosing.

Tsuyoshi Fukuda, PhD

[Tsuyoshi Fukuda, PhD](#), successfully finalized the data collection phase for his study "Novel Pharmacokinetic-Pharmacogenetic Approach for Morphine Treatment in Neonates" supported by a CCTST T1 Pilot Collaborative Studies (PCS) Grant. Inadequate pain control in neonates is an important clinical concern with potential long adverse consequences. By studying the pharmacokinetics and pharmacogenetics of morphine in neonates and developmental changes in pharmacokinetics related enzymes, we will gain insight in the factors that cause some patients to respond well whereas others have inadequate pain control or adverse drug reactions.

Two research fellows, for whom Drs. Fukuda and Vinks served as mentors, were awarded with the President's Trainee Award during the 2015 Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics.

Chie Emoto, PhD

Chie Emoto, PhD developed an innovative physiologically-based pharmacokinetic (PBPK) model of sirolimus (mTOR inhibitor) for neonates and small infants using data obtained from a concentration-controlled Phase II clinical study in pediatric patients with vascular anomalies (PI: [Denise Adams, MD](#)). This predictive computer model helps physicians fine-tune doses to maintain target sirolimus concentrations in neonates based on patients' physiological parameters. This study

has been published in *CPT Pharmacometrics Systems Pharmacology*, which is an official journal of the [American Society of Clinical Pharmacology and Therapeutics](#).

Significant Publications

Dong M, **Fukuda T**, Cox S, de Vries MT, Hooper DK, Goebel J, **Vinks AA**. Population Pharmacokinetic-Pharmacodynamic Modelling of Mycophenolic Acid in Paediatric Renal Transplant Recipients in the Early Post-Transplant Period. *Br J Clin Pharmacol*. 2014 Nov;78(5):1102-12.

Mycophenolic acid (MPA) exhibits wide between- and within-patient pharmacokinetic (PK) variability. We developed an integrated population pharmacokinetic-pharmacodynamic (PK-PD) model to simultaneously describe the relationship between MPA dose, MPA plasma concentration, and IMPDH inhibition as biomarker of immunosuppression in pediatric kidney transplant patients. Targeting IMPDH inhibition as a biomarker of MPA induced immunosuppression, when used in an integrated PK-PD fashion, may provide a better predictor of clinical outcome. The developed population PK-PD model will be used to establish a Bayesian algorithm to allow PK-PD guided personalized dosing.

Smits TA, Cox S, **Fukuda T**, Sherbotie JR, Ward RM, Goebel J, **Vinks AA**. Effects of Unbound Mycophenolic Acid on Inosine Monophosphate Dehydrogenase Inhibition in Pediatric Kidney Transplant Patients. *Ther Drug Monit*. 2014 Dec 2014;36(6):716-23.

This study provides a simple method for the measurement of non protein bound MPA and a reasonable estimate of the concentration-effect relationship. The good correlation between the total and free MPA concentrations suggests that routine measurement of unbound MPA to characterize mycophenolate pharmacokinetic and pharmacodynamic does not seem warranted.

Emoto C, **Fukuda T**, Johnson TN, Adams DM, **Vinks AA**. Development of a Pediatric Physiologically Based Pharmacokinetic Model for Sirolimus: Applying Principles of Growth and Maturation in Neonates and Infants. *CPT: Pharmacometrics Syst Pharmacol*. 2015 Feb;4(2):e17.

There is an unmet clinical need for the development of the age-appropriate dosing guidelines for m-TOR inhibitors such as sirolimus in pediatric patients with cancer and blood related diseases. We studied the age-related maturation of sirolimus clearance using pediatric in vivo data, demonstrated age-dependent in vitro sirolimus metabolism associated with CYP3A metabolic activity, and developed a pediatric PBPK model to predict sirolimus exposure across the pediatric age spectrum. This approach leverages limited clinical observations and serves as a practical application for the establishment of age-appropriate dosing of sirolimus in pediatric patients.

Emoto C, **Fukuda T**, Mizuno T, Cox S, Schniedewind B, Christians U, Widemann BC, Fisher MJ, Weiss B, Perentesis J, **Vinks AA**. Age-Dependent Changes in Sirolimus Metabolite Formation in Patients with Neurofibromatosis Type 1. *Ther Drug Monit*. 2015 Jun;37(3):395-9.

This study suggests that the age-dependent changes in sirolimus clearance can be explained by parallel increases in CYP3A metabolic capacity with age, most likely due to liver and intestinal growth. These findings will help facilitate the development of age-appropriate dosing algorithms for sirolimus in infants and children.

Venkatasubramanian R, **Fukuda T**, Niu J, Mizuno T, Chidambaran V, **Vinks AA**, Sadhasivam S. ABCC3 and OCT1 Genotypes Influence Pharmacokinetics of Morphine in Children. *Pharmacogenomics*. 2014 Jul;15(10):1297-309.

Large inter-individual variability in morphine pharmacokinetics clearly contributes to variability in morphine analgesia and adverse events. We studied the influence of body weight, genetic polymorphisms, race and sex on morphine

clearance and metabolite formation in 220 children undergoing outpatient adenotonsillectomy. Our data suggest that besides body weight, transporter genotypes (OCT1 and ABCC3) involved play a significant role in the pharmacokinetics of intravenous morphine and its metabolites in children.

Division Publications

1. Dong M, Fukuda T, Cox S, de Vries MT, Hooper DK, Goebel J, Vinks AA. **Population pharmacokinetic-pharmacodynamic modelling of mycophenolic acid in paediatric renal transplant recipients in the early post-transplant period.** *Br J Clin Pharmacol.* 2014; 78:1102-12.
2. Emoto C, Fukuda T, Johnson TN, Adams DM, Vinks AA. **Development of a Pediatric Physiologically Based Pharmacokinetic Model for Sirolimus: Applying Principles of Growth and Maturation in Neonates and Infants.** *CPT: Pharmacometrics & Systems Pharmacology.* 2015; 4:e17.
3. Emoto C, Fukuda T, Mizuno T, Cox S, Schniedewind B, Christians U, Widemann BC, Fisher MJ, Weiss B, Perentesis J, Vinks AA. **Age-dependent changes in sirolimus metabolite formation in patients with neurofibromatosis type 1.** *Ther Drug Monit.* 2015; 37:395-9.
4. Fouladi M, Perentesis JP, Wagner LM, Vinks AA, Reid JM, Ahern C, Thomas G, Mercer CA, Krueger DA, Houghton PJ, Doyle LA, Chen H, Weigel B, Blaney SM. **A Phase I Study of Cixutumumab (IMC-A12) in Combination with Temsirolimus (CCI-779) in Children with Recurrent Solid Tumors: A Children's Oncology Group Phase I Consortium Report.** *Clin Cancer Res.* 2015; 21:1558-65.
5. Hahn A, Frenck RW, Jr., Zou Y, Vinks AA. **Validation of a pediatric population pharmacokinetic model for vancomycin.** *Ther Drug Monit.* 2015; 37:413-6.
6. Nakamaru Y, Emoto C, Shimizu M, Yamazaki H. **Human pharmacokinetic profiling of the dipeptidyl peptidase-IV inhibitor teneligliptin using physiologically based pharmacokinetic modeling.** *Biopharm Drug Dispos.* 2015; 36:148-62.
7. Nehus EJ, Mouksassi S, Vinks AA, Goldstein S. **Meropenem in children receiving continuous renal replacement therapy: clinical trial simulations using realistic covariates.** *J Clin Pharmacol.* 2014; 54:1421-8.
8. Rasmussen-Torvik LJ, Stallings SC, Gordon AS, Almoguera B, Basford MA, Bielinski SJ, Brautbar A, Brilliant MH, Carrell DS, Connolly JJ, Crosslin DR, Doheny KF, Gallego CJ, Gottesman O, Kim DS, Leppig KA, Li R, Lin S, Manzi S, Mejia AR, Pacheco JA, Pan V, Pathak J, Perry CL, Peterson JF, Prows CA, Ralston J, Rasmussen LV, Ritchie MD, Sadhasivam S, Scott SA, Smith M, Vega A, Vinks AA, Volpi S, Wolf WA, Bottinger E, Chisholm RL, Chute CG, Haines JL, Harley JB, Keating B, Holm IA, Kullo IJ, Jarvik GP, Larson EB, Manolio T, McCarty CA, Nickerson DA, Scherer SE, Williams MS, Roden DM, Denny JC. **Design and anticipated outcomes of the eMERGE-PGx project: a multicenter pilot for preemptive pharmacogenomics in electronic health record systems.** *Clin Pharmacol Ther.* 2014; 96:482-9.
9. Rosen MJ, Minar P, Vinks AA. **Review article: applying pharmacokinetics to optimise dosing of anti-TNF biologics in acute severe ulcerative colitis.** *Aliment Pharmacol Ther.* 2015; 41:1094-103.
10. Smits TA, Cox S, Fukuda T, Sherbotie JR, Ward RM, Goebel J, Vinks AA. **Effects of unbound mycophenolic acid on inosine monophosphate dehydrogenase inhibition in pediatric kidney transplant patients.** *Ther Drug Monit.* 2014; 36:716-23.

11. Venkatasubramanian R, Fukuda T, Niu J, Mizuno T, Chidambaran V, Vinks AA, Sadhasivam S. **ABCC3 and OCT1 genotypes influence pharmacokinetics of morphine in children.** *Pharmacogenomics*. 2014; 15:1297-309.
 12. Weiss B, Widemann BC, Wolters P, Dombi E, Vinks A, Cantor A, Perentesis J, Schorry E, Ullrich N, Gutmann DH, Tonsgard J, Viskochil D, Korf B, Packer RJ, Fisher MJ. **Sirolimus for progressive neurofibromatosis type 1-associated plexiform neurofibromas: a neurofibromatosis Clinical Trials Consortium phase II study.** *Neuro Oncol*. 2015; 17:596-603.
 13. Wiles JR, Isemann B, Ward LP, Vinks AA, Akinbi H. **Current management of neonatal abstinence syndrome secondary to intrauterine opioid exposure.** *J Pediatr*. 2014; 165:440-6.
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Faculty, Staff, and Trainees

Faculty Members

Alexander A. Vinks, PharmD, PhD, Professor

Leadership Division Director; Fellowship Director; Co-Director, Genetic Pharmacology Service; 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, Assistant Professor

Leadership Assistant Professor

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

Tsuyoshi Fukuda, PhD, Associate Professor

Leadership 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 clinical trials methodology; epilepsy.

Senthikumar Sadhasivam, MD, MPH, 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, University of Pennsylvania, Philadelphia, PA
- **Joshua Euteneuer, MD**, 2010, University of Nebraska Medical Center, Omaha, Nebraska
- **Andrea Hahn, MD**, 2008, Ohio State University, Columbus, Ohio
- **David Hahn, PhD**, 2014, University of Cincinnati, Cincinnati, Ohio

- **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, University of Massachusetts, Amherst, MA

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 HD069054	5/16/2011-4/30/2016	\$194,526
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Pharmacokinetic Studies of Tacrolimus in Transplant Patients

Food and Drug Administration(University of Cincinnati)

U01 FD004573	9/15/2012-9/14/2015	\$40,997
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Pilot Trial of Bumetanide for Neonatal Seizures

National Institutes of Health(Children's Hospital Boston)

R01 NS066929	8/2/2010-6/30/2015	\$5,000
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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	9/26/2013-9/25/16	\$116,474
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Current Year Direct	\$356,997
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Total	\$356,997
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Systems Pharmacology Approach Leads to Precision Drug Dosing Algorithm for Neonates, Infants and Children



Alexander Vinks, PharmD, PhD

PUBLISHED ONLINE FEB. 4, 2015

CPT: Pharmacometrics and Systems Pharmacology

A predictive computer model developed at Cincinnati Children’s is helping doctors fine-tune the doses of drugs they give to neonates, infants and children, based on specific measurements on how their bodies metabolize and respond to the drugs.

It is a far better system, says lead author Alexander Vinks, PharmD, PhD, Director of Clinical Pharmacology, than the traditional practice of dosing drugs for infants and neonates using a kilogram-to-milligram scale based on a child’s weight — a scaled-down but inaccurate version of adult doses that are downsized and applied to tinier bodies.

“It’s always been a tricky question, one that’s very difficult to predict at any given age: how much of a drug to give to a two-week old infant vs. a year-and-a-half-old toddler,” says Vinks. “The moment a child is born, all these physiological systems kick in, but we haven’t known the pace and maturation levels of various systems until we looked at data from various studies.”

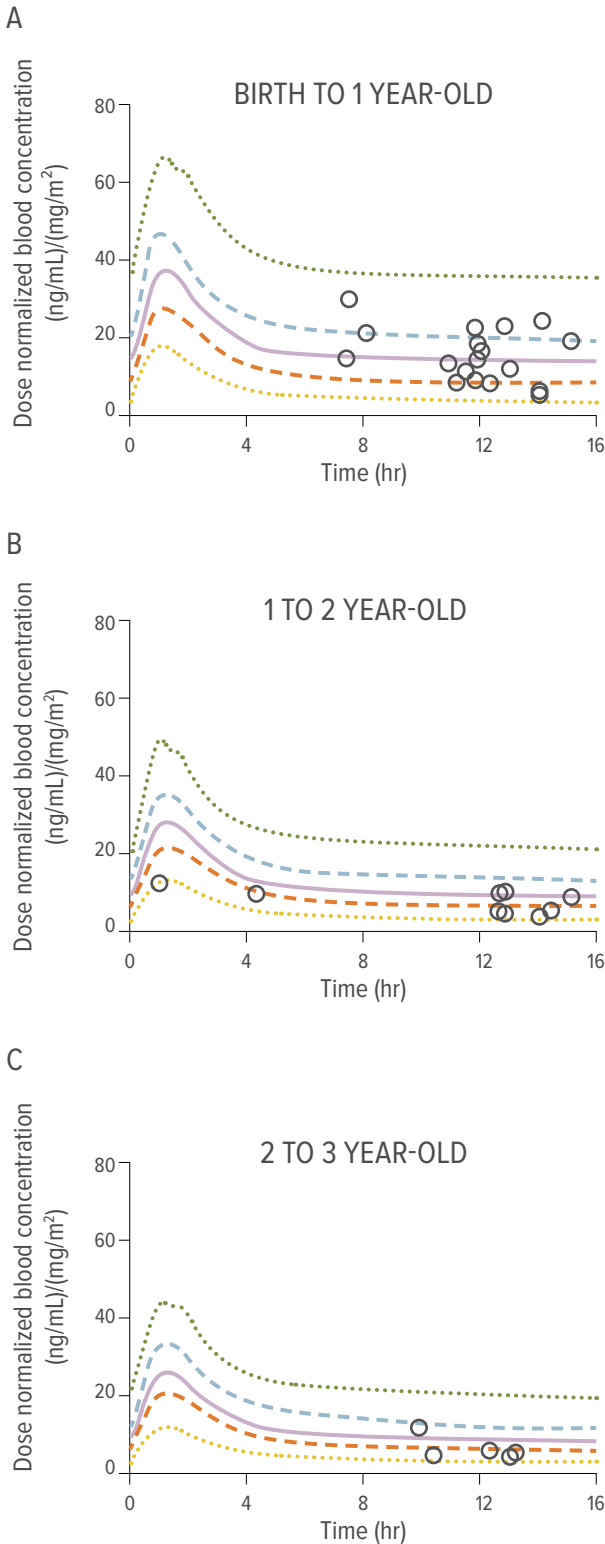
Vinks and colleagues participated in a concentration-controlled clinical trial of sirolimus, a drug increasingly used to treat vascular abnormalities but not extensively studied in children. Researchers started a dose and measured sirolimus levels. Next, enzyme measurements reflective of each patient’s liver enzyme CYP3A activity, known to metabolize drugs, were combined with other data, including the child’s age, weight, gender, ethnicity, height, sirolimus concentrations, dosing regimens and other medications. Data from three studies were combined to create an algorithm — still being refined — to pinpoint accurate drug dosing levels. Findings appeared Feb. 4, 2015, in *CPT: Pharmacometrics and Systems Pharmacology*.

“It’s a very sophisticated way of using state-of-the-art techniques to tease out data for specific drug doses — a sophisticated way of personalized precision dosing,” according to Vinks. His division is working on similar algorithms for methadone and morphine, and receiving inquiries from the around the world about pediatric doses for other drugs.

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Emoto C, Fukuda T, Johnson TN, Adams DM, Vinks AA. Development of a Pediatric Physiologically Based Pharmacokinetic Model for Sirolimus: Applying Principles of Growth and Maturation in Neonates and Infants. *CPT Pharmacometrics Syst Pharmacol.* 2015;4(2):127-134.



These graphs compare observed sirolimus concentrations with simulated concentration-time profiles using a pediatric physiologically based pharmacokinetic model based on healthy children aged birth to 1 year (a), 1-2 years (b), and 2-3 years (c). In the simulations, sirolimus was administered orally at 1.0 mg/m² twice a day for 30 days. Each bold line shows the median; dashed lines indicate 25 to 75 percentiles; dotted lines show 5 to 95 percentiles. The circles represent observed concentrations in each patient.