Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
National Institute of General Medical Sciences (NIGMS)
National Institutes of Health (NIH)
NIGMS-NICHD and NICHD T32 Programs in Pediatric Clinical Pharmacology
Meeting of the T32 Trainees
September 13–14, 2012
Executive Plaza North
Room H
6130 Executive Boulevard
Rockville, MD

Introductions

George Giacoia, M.D., Medical Officer, Obstetric and Pediatric Pharmacology Branch (OPPB), NICHD, NIH

Dr. Giacoia welcomed the participants to the meeting, emphasizing that the new program in pediatric clinical pharmacology is part of a larger initiative to advance pediatric therapeutics in order to stimulate interdisciplinary collaboration among clinical translational and basic researchers in pediatric therapeutics and to enable the development of pediatric programs within the adult pharmacology programs. The goal is to encourage interaction among the specialties and between adult and pediatric specialties, which currently does not exist. One of the initiatives to facilitate this interaction is the comparison of chronic conditions that affect both children and adults—asthma, diabetes, and mood disorders—using groups made up of top-level experts in those fields; T32 fellows will be ad hoc members in these groups.

Overview of Activities to Advance Pediatric Therapeutics Under the Best Pharmaceuticals for Children Act (BPCA)

Anne Zajicek, Pharm.D., M.D., Branch Chief, OPPB, NICHD, NIH

Dr. Zajicek gave background information about the BPCA, the goal of which is to improve pediatric labeling by funding pediatric clinical pharmacology studies to yield data to submit to the U.S. Food and Drug Administration (FDA). Prioritizing adequacy of necessary infrastructure was added to the 2007 BPCA legislation: There was no developed mechanism in place to conduct the clinical trials, and there were not sufficient numbers of experts to conduct these trials. To address the lack of a clinical trials network structure, the NIH developed the Duke Pediatric Clinical Trials Network (PTN). The PTN's purpose is to manage and perform pediatric clinical trials through management of the clinical trials sites, design of the studies and performance of the clinical pharmacology tasks, recruitment of patients for the studies, development of formulations for research purposes for the clinical trials (not to manufacture), data analysis, and device development and validation. The Pediatric Pharmacology Branch at the NIH consists of three components to address the need for experts trained in pediatric clinical pharmacology to design, perform, and analyze the clinical trials and treat patients:

- Research: U54 Basic/Translational Research in Pediatric Developmental Pharmacology centers

- Training in clinical pharmacology: T32, F31, F32 programs
- Service: PTN preclinical studies, clinical studies, formulations, device development validation, clinical pharmacology.

Dr. Zajicek said that she, Dr. Giacoia, and Dr. Richard Okita are available to answer any questions about grants or training.

Remarks

Richard Okita, Ph.D., Program Director, NIGMS, NIH

Dr. Okita thanked Dr. Giacoia for his leadership in this effort and stressed his availability to assist the fellows in their work. He shared that the NIH Director's New Innovator Award program is a way the fellows might be able to explore their ideas and might be an alternative to R01 funding, and the award program is an area he would like to see built up in pediatrics.

The Critical Need for Trained Pediatric Clinical Pharmacologists and the Impact on Pediatric Therapeutics

Jeffrey Blumer, M.D., Ph.D., The Toledo Children's Hospital

Dr. Blumer noted that the current paradigm of clinical training is oriented toward the patient: The patient has a chief complaint; a history is taken that includes information about past medical encounters, family, and factors in addition to the present illness; there is a physical exam; and that information leads to a differential diagnosis. After the differential diagnosis, laboratory and other testing is conducted, leading to a refined diagnosis, which enables the physician to develop a plan that will consist of either drug treatment or surgery. Dr. Blumer noted that this traditional approach to therapeutics can be a problem. Therapeutics is reduced to drug-disease matching, drug selection is inextricably linked to the diagnostic process, and treatment is largely a menu of designated fixed-dose options. Such approaches often preclude considerations of mechanisms of action and variability in drug disposition and response—all patients get the same dose.

History of Clinical Pharmacology. Clinical pharmacology began as a bridging discipline between classical pharmacology and clinical medicine. The thalidomide tragedy of 1961 was the point at which this bridging began in the United States, after which there were the first NIH-funded centers of excellence in pharmacology, development of laboratory methods to measure drug concentrations in patient samples, and adoption of the approaches originated by Harry Gold and Walter Modell, including the double-blind design for clinical trials and the use of "effect kinetics." These changes resulted in the recognition that most adverse drug reactions occur with commonly used drugs rather than new ones; they are generally dose-related rather than idiosyncratic and are preventable events. These preventable causes include the following:

- Inappropriate polypharmacy
- Failure of prescribing physicians to establish and adhere to clear therapeutic goals
- Failure of medical personnel to attribute new symptoms or changes in laboratory test results to drug therapy
- Lack of priority given to the scientific study of adverse drug reaction mechanisms

- The general ignorance of basic and applied pharmacology and therapeutic principles.

To address these problems, the development of the clinical pharmacology discipline was focused on optimizing use of existing medications and on the scientific study of drugs in humans, specifically the evaluation of the safety and efficacy of currently available drugs and the development of new and improved pharmacotherapy. Prior to the late 1970s, most drug-related legislation in the United States had its origins in adverse drug reactions in children, but none resulted in a mandate to study drugs in the pediatric population. One important realization that came out of this, however, was that children are not "little adults"; that is, children are different. Whereas all pediatric dosing processes—Fried's Rule, Clark's Rule, and Young's Rule—had been based on the adult dose, there was a movement toward focusing on pediatric pharmacology, recognizing that, as the American Academy of Pediatrics (AAP) Committee on Drugs statement said, "it is unacceptable that a population that is growing, developing, and inherently highly variable would not be studied." Because of this lack of study, drugs are used off-label in children, which is problematic because of the lack of age-related dosing guidelines and adverse effect profiles and because of the problems that are unique to children due to developmental and growth issues.

By 1990, 75–80 percent of drugs were not labeled as safe and effective for infants and children, off-label use was the norm, there was little awareness among practitioners that prescribing for children was not evidence-based, and there was little political or public awareness of the problem. Additionally, the feasibility of drug study in children was questioned because of a lack of economic incentive, perception of greater liability, a small patient population, few trained clinical investigators, and few pediatric design paradigms. There was a knowledge gap in the pediatric therapeutic research environment because of ethical concerns in studying drugs in children, very limited populations for certain diseases, logistical and technical difficulties in conducting pediatric trials, a belief that dosing could simply be determined by weight (based on the adult dose), a lack of accepted endpoints and validated pediatric assessment tools, and limited marketing potential compared to adults. This knowledge gap had serious consequences:

- Most prescriptions for children are in fact unsanctioned experiments.
- Drug effectiveness in children is assumed but largely unsubstantiated.
- Safety profiles of drugs in children are seldom defined.
- Drug effects on normal growth and development remain uninvestigated.
- Children are excluded from the benefits of therapeutic advances. However, drug therapy in children may have unexpected consequences, including death.

In order to ensure the availability of safe and effective drug therapy for infants, children, and adolescents, drugs must be studied in that population.

Currently, new drugs developed for diseases occurring in adults and children are used in children. Pediatric doses are more likely to be ineffective than toxic; this shifts the whole paradigm of risk/benefit against the patient. Anything unusual will be blamed on the new drug, and the absence of labeling or inclusion of an "orphan clause" does not limit liability.

Pediatric clinical pharmacology as it stands needs to integrate developmental pharmacology and pediatric pharmacology. Developmental pharmacology describes the use of drugs and chemical agents to elucidate the ontogeny of physiological processes. Pediatric pharmacology involves the study of therapeutic agents in infants, children, and adolescents and involves going from "bench to bedside" and "bedside to bench." The key guiding principles in pediatric clinical pharmacology are that children are neither small adults nor juvenile animals and that drug pharmacodynamics (PD) and pharmacokinetics (PK) demonstrate profound postnatal age dependency. The scope of pediatric clinical pharmacology involves prenatal drug exposures, therapy for uniquely pediatric clinical entities, and the extension of therapies developed for adult patients to pediatric patients. Reasons to perform clinical trials in children are to enable the determination of age-appropriate dosing strategies, developmentally appropriate safety profiles, and drug efficacy. Challenges in conducting these pediatric clinical trials are protocol design, relatively small patient numbers, local or regional practice standards differences, the conflict between clinical care and clinical research, the ethical considerations of conducting trials on children, and obtaining consent/assent.

To meet the manpower needs for addressing pediatric therapeutics, clinician scientists with certain characteristics need to be developed:

- An in-depth understanding of the unique language based on pharmacology and therapeutics
- An understanding of the ontogeny of the processes that determine drug disposition and drug action
- Pediatric therapeutics trial experience
- A strong tradition of academic-industry collaboration
- Multidisciplinary collaborations, including subspecialists, general practitioners, and basic scientists.

The Ontogenetic Determination of Drug Dosing. There are significant differences in PK between children and adults in terms of the ontogenetic determination of drug dosing. Age is a significant variable due to changes in body composition, endogenous ligands for protein-binding sites, nature and activity of drug-metabolizing enzymes, and renal function. Dosing requirements are somewhat counterintuitive in that higher mg/kg doses are usually required. Dr. Blumer noted, however, that the next frontier is PD. Age is a significant variable in determining drug action due to changes in receptor number, receptor affinity, and autonomic tone. Also, end-point determinations must be modified to meet age-appropriate targets, and safety profiles tend to demonstrate that infants and children are less likely to experience adverse events. Finally, age is a significant variable in drug formulation because of the need for liquid dosage forms; problems with excipients; palatability, which determines compliance; and the different palates children have compared to adults. Solid dosage forms may be problematic even in early adolescence, inhaled dosage forms present challenges to coordination for young children, and children do not like injections.

The transition from "drug-oriented" to "patient-oriented" research reintroduces basic pharmacology principles into pediatric clinical trials in terms of dose-response relationships, the ontogeny of absorption/distribution/metabolism/excretion (ADME) processes, the power of modeling, molecular determinants of drug response, and developmental differences in pediatric

populations in terms of both efficacy and toxicity. This led to the transition from single subspecialty-based investigators to multidisciplinary teams and the creation of the Pediatric Pharmacology Research Units (PPRUs), as well as the recognition of unmet medical needs in neonatal therapeutics, adverse drug reactions, central nervous system (CNS) agents, analgesia/sedation, obesity, cancer therapeutics, antimicrobials/anti-inflammatories, and neuroprotection. Application of pharmacology allowed scientists to address the molecular determinants of drug responsiveness, moving from studying disease to studying mechanisms. Ultimately, this provides for an emerging integrative strategy that can equate pediatric clinical pharmacology with the development of personalized medicine—bench-to-bedside and bedside-to-bench translational approaches that embrace all with the common language of pharmacology.

Lessons Learned Regarding Pediatric Drug Therapy.

- Historically, drugs have been used in children without the same level of evidence as has been obtained for adults; the data confirm that such an approach is not good public policy.
- Children are even more dynamic and variable than anticipated.
- New legislation is having a positive impact on development of therapies for children.
- These pediatric initiatives have identified some gaps and how much is not known.
- Children have unnecessary exposure to ineffective drugs.
- There has been both ineffective dosing and overdosing of effective drugs.
- Undefined unique pediatric adverse reactions are recognized.
- Drugs can affect growth and behavior.
- PK is more variable, even within the pediatric population, than anticipated.
- Adverse drug reactions that are pediatric-specific will not be defined without pediatric studies.
- Trial designs are being modified as more is learned from submitted studies.
- Ethical issues have to be reassessed from the pediatric perspective.
- Safety studies of sufficient duration and longer term follow-up studies remain problematic.

Resolution of the Knowledge Gap. To address the knowledge gap that currently exists in pediatric pharmacology, Dr. Blumer made several recommendations:

- Carefully planned clinical research studies are essential.
- Physicians in pediatric specialties must be trained to effectively conduct these studies.
- Priority areas for investigation must be identified.
- Fiscal resources must be allocated to these areas.
- An infrastructure to support these efforts must be established.

There is no shortage of need for future study in pediatric clinical pharmacology—in CNS diseases, cardiovascular diseases, and respiratory diseases. Pediatric clinical pharmacology has evolved from a single-person outpost in internal medicine to pediatricians who are interested in drugs working to develop a delivery system that is designed and integrated to address pediatric therapeutics.

Introductory Remarks

Scott Waldman, M.D., Ph.D., Thomas Jefferson University

Dr. Waldman thanked Dr. Giacoia for his work in this area, noting that pediatric clinical pharmacology, pediatric pharmacology, and developmental pharmacology have been underemphasized, underfunded, and underappreciated for many years. The participants of this meeting have been driving the development of this field. The goal of this meeting is to create collaboration among clinical pharmacologists—to learn who is who, who has the tools that might be useful, and to forge collaborations and relationships. During this two-day meeting there will be panels made up of experts who can speak to clinical pharmacology from different perspectives, so as to give everyone the opportunity to learn about the application of pharmacometrics to pediatric therapeutics and clinical pharmacology in a variety of ways.

Round Table Discussion: T32 Fellows Training Issues
Working Knowledge of "-omics" Technology Unrelated to Fellows Research Project

Moderator: J. Steven Leeder, Pharm.D., Ph.D., Children's Mercy Hospitals and Clinics

Dr. Leeder opened the discussion by giving some basic ideas to prompt questions. He noted that "cool tools are no substitute for an elegant question," so that first someone comes up with a research question and then looks for the right tools to answer that question. The availability of "-omic" technologies has led to a shift away from narrowly focused, individual investigator-driven research labs to what is now called "big science"—where there is a drift away from hypothesis-driven research toward exploratory research. While it may be unreasonable to expect that individuals can become an expert in all areas, it is still important to become familiar with these new tools in order to be able to select the right one for the question of interest.

Dr. Leeder gave some references to assist the fellows in getting familiar with "-omic" technologies:

- **Genomics**
  - Majewski, et al. *J Med Genet.* 2011;48:580–589. (Good overview of genomics)
  - Cooper, Shendure. *Nat Rev Genet.* 2011;12:628–640. (Series of papers on applications of next-generation sequencing)
  - Alkan, et al. *Nat Rev Genet.* 2011;12:363–375.
- **Transcriptomics**
  - Martin, Wang. *Nat Rev Genet.* 2011;12:671–682.
  - Trapnell, et al. *Nat Protocols.* 2012;7:562–578. (Helpful for those interested in the technologies when analyzing RNA-Seq data)
- **Metabolomics**
  - Kaddurah-Douk, et al. *Ann Rev Pharmacol Toxicol.* 2008;48:653–683. (Good overview of metabolomics)
  - Keun. *Pharmacol Ther.* 2006;109:92–106. (Overview of platforms used for metabolomics research)
- **Integrative Analysis**
  - Kasarkis, et al. *Pharmacogenomics.* 2011;12:1695–1715.
  - Zhao, Iyengar. *Ann Rev Pharmacol Toxicol.* 2012;52:505–521.

Dr. Leeder asked the fellows how many were currently using any kind of "-omic" technology. Two fellows indicated they were. Dr. Waldman asked whether anyone else was planning to use "-omic" technologies. Approximately four more fellows indicated they were. Dr. Waldman noted that all of his fellows at Thomas Jefferson University Jefferson Medical College are planning on using "-omic" technologies in adult clinical pharmacology. Dr. Blumer asked what implications this has on pediatrics. Dr. Waldman noted that the use of "-omic" technologies is not filtering into the pediatric field. It may be that the technology is available at the institution but not the intellectual capital because it has not been taught, so it has not been integrated into the questions being researched in pediatrics. Dr. Waldman stressed that awareness of "-omic" ideas should lead to cutting-edge questions for contemporary approaches to pediatric clinical pharmacology. Dr. Leeder said that "-omic" technologies can help when taking a profiling approach that might change with time, which is important for pediatric issues. Knowing what is changing and what is outside the normal range can track with large datasets, which is what "-omic" technologies can help with.

Needed Knowledge of Pharmacometrics

Moderator: Sander Vinks, Pharm.D., Ph.D., Cincinnati Children's Hospital Medical Center

The pharmaceutical companies were a driving force behind the introduction of pharmacometrics in drug development. Pfizer is probably the first company that began to use quantitative approaches in pharmacology, which developed into what is now known as pharmacometrics. There is a tremendous opportunity to apply pharmacometrics to patient care. Pharmacometrics involves analyzing previous data, summarizing that data, and applying that new information to future patients. Pharmacometrics can benefit treatment by helping to:

- Describe and understand drug PK/PD behavior in children and adults
- Collect informative data to use as Bayesian priors for designing individualized dosing regimens—turning information into knowledge that can be applied at the bedside
- Predict and therefore control the system (that is, the target site concentration)
- Achieve a paradigm shift in the way individualized therapeutics are delivered.

Pharmacometrics can give important information to assist in study design, such as correct dosing information to address the effect of growth and maturation, the required number of patients for a statistically robust estimation of PK/PD relationships, the number of samples needed per patient, and the optimal times for sampling.

Pharmacometrics Tools. There are many pharmacometrics tools available, with advantages and disadvantages to each:

- **Curve-fitting programs (one subject at a time); rich data:** ADAPT, WinNonlin, SAAM, Kinetica
- **Nonlinear mixed-effects modeling programs; rich and sparse data:** NONMEM, Pmetrics, Monolix, Phoenix NPLM, WinBUGS, S-Adapt, Kinetica, SAS, NLME (S-Plus
- **Bayesian and simulation software; sparse data:** Abbotbase, MW/Pharm, USC*PACK, Multiple Model (most common in pediatric clinical pharmacology)
- **Simulation software (mechanistic model building):** Berkeley Madonna, Model Maker, acslXtreme, Stella, Gepasi

- **(Population) optimal design and clinical trial simulation:** ADAPT, S-ADAPT, PFIM, WinPOPT, POPT, PKStaMP, PopDes, POPED, Pharsight Clinical Trial Simulator.

Dr. Waldman asked the fellows who were currently using pharmacometrics in their research whether they were at centers where pharmacometrics was routinely used. Many were not. Dr. Waldman encouraged the fellows who are not at centers where pharmacometrics is used frequently to create linkages with those centers that do in order to increase the amount and speed of progress in their research.

Mentoring Issues: Advantages and Limitations

Moderator: Kim Brouwer, Pharm.D., Ph.D., University of North Carolina (UNC) Eshelman School of Pharmacy

Dr. Brouwer noted that mentoring has an important influence on personal development, career guidance, and research productivity and as such is a catalyst for career success. Qualities of a good mentor include availability, openness, timeliness, and the ability to communicate and motivate. A mentoring team can be more useful than a single mentor by increasing the scope and breadth of input and assistance available and to prevent the mentee from becoming a "clone" of the mentor. Mentors do not need to be at the mentee's institution; creating linkages with mentors at other institutions can be just as helpful. Qualities of a good mentee include being receptive to feedback and acting on that feedback, being motivated and proactive, and setting out goals and objectives at the beginning of the mentorship. It is important to have a mentoring plan that specifies the frequency of meetings and the roles of mentors, objectives and expectations, process for progress reports, and success criteria. The mentee should know his or her strengths and weaknesses in order to choose a mentoring team.

Introduction to Pharmacometrics: Regulatory Drivers for Pharmacometric-Related Analyses: Impact of PIPs, Protocol Submissions, and Labeling Requirements for Pediatric Drug Development

Jeffrey Barrett, Ph.D., The Children's Hospital of Philadelphia (CHOP)

Pharmacometrics can be defined as the science that quantifies drug, disease, and trial information to aid efficient drug development, regulatory decisions, and rational drug treatment in patients. It involves the disciplines of clinical pharmacology, statistics, pharmacology, medicine, computational methods, and engineering and many times involves computer science, ethics, pharmaceutics, health economics and marketing, and regulatory science. Multiple "deliverables" exist under the umbrella of pharmacometrics, including PK/PD, dose individualization, optimal experimental design, clinical trial design, and pharmacogenetics. Interrelated as well as distinct objectives often exist for specific application. Pharmacometrics is very reliant on "prior knowledge" to fulfill study/experimental goals, and inputs to models can be diverse and directed to specific (individual) patients or populations. Modeling and simulation techniques are behind much of the actual pharmacometric deliverables. The complexity of models can be accommodated by various techniques and approaches, and the simulation framework permits assumption testing, which is critical for pediatrics, where much emphasis is placed on "leveraging" adult experience. A model can be defined as a mathematical expression of

conceptualized process relating design and process variables to outcomes. A simulation is made up of conditions and scenarios that are evaluated to judge parameter sensitivity, process design, covariate sampling distributions, and other factors that may affect response of the test system, such as an experiment, a trial, and so on. The integration of modeling and simulations is essential for decision making about the number and nature of subsequent experiments. The modeling process is circular and dynamic, and a model is, in itself, only an information-dependent representation of the physical system. Likewise, the modeling process must be fed by additional/subsequent data and knowledge about the experimental design, the features or structure of the model, the sampling population, and the complement covariate distributions.

Simulations have specific objectives:

- Model evaluations: To verify model performance across the range of expected outcomes and parameter space
- Experimental design: To examine designs versus outcome space against study objectives and hypotheses
- Experimental conditions: To examine the sensitivity of model performance and outcomes to input and sampling designs
- Data pooling: To examine the sensitivity of model performance and outcomes to data from various studies and experiments
- Population evaluation: To verify model performance across the range of expected populations for structural compatibility
- Covariate evaluation: To verify model performance across the range of expected covariate space.

The choice of approach and technique for modeling and simulations depends on the answers to the following questions:

- Deterministic or stochastic: Does the model contain stochastic components?
- Static or dynamic: Is time a significant variable?
- Continuous or discrete: Does the system state evolve continuously or only at discrete points in time?
  - Continuous: classical mechanics
  - Discrete: queuing, inventory, machine shop models.

The use of sparse sampling techniques and leveraging what is possible to obtain from other sources—modeling—is essential in pediatrics due to the often limited availability of the patient population, constraints on blood collection volume, limited funds to support pediatric drug development, and reliance on adult clinical experience.

Dr. Barrett stressed that if the goal is to submit any new molecular entities or older drugs for labeling, it is important to do the pharmacometrics work because the FDA has a responsibility to protect the American public, reduce risks, examine population extremes, and ensure quality in both the product and the decision making. Pharmacometrics will be the basis for the confidence dose and frequency of dosing considerations; expected variability in PK, PD, and outcomes; dose adjustments; label justification; warnings; and metrics for judging clinical benefit.

The FDA's concerns about the drug development decision process center around the idea that marketing has trumped science and that "champions" for certain drugs trump team recommendations. The FDA believes better decisions can be made regarding trial design, dose response, safety signals, market value, and labeling. The FDA proposal is for model-based drug development, deriving relationships between activity and toxicity for a drug relative to exposure and integrating them to identify the best dose as well as to obtain information about go/no go criteria, labeling, formulations, drug combinations, and pediatrics. The modeling cycle consists of the following:

- Build the disease and drug model, which gives information about the natural history of the disease and how the intended drug actions overlay the population.
- Extract clinical trial information including baseline effect/model, placebo model, dropout model, design, and patient demographics.
- Simulate scenarios through trial design, patient selection, dosage regimen, sample size, sampling times, endpoints, and analysis.
- Plug in sponsor data to decide go/no go and trial design.

The FDA has a new pediatric labeling information database, where all the labeling guidance available in pediatrics is now collated.

To encourage drug companies to provide pediatric information at an early stage, the FDA required submission of a Pediatric Investigational Plan (PIP) if the drug had a potential pediatric application. The PIP is a strategic document:

- Overall strategy proposed for pediatric development by the applicant (for example, proposed indication, age group, possible extrapolation, interrelation, and existing data)
- Strategy in relation to quality development (need for formulation)
- Strategy in relation to nonclinical (for example, specific pharmacology/toxicity studies)
- Strategy in relation to clinical aspects (for example, PK, efficacy/safety, and long-term safety)

Dr. Barrett illustrated how pharmacometrics has become part of the labeling process with an example of topiramate, leading to these conclusions:

- Pharmacometric approaches are increasingly employed to support pediatric research and development.
- The adoption and use of appropriate pharmacometric techniques is a regulatory expectation for pediatric submissions.
- The use of appropriate pharmacometric techniques is behind many of the recent labeling changes and dosing guidance in children.

Discussion of Trainees' Research

Jacob Brown, Pharm.D.; Children's Mercy Hospitals and Clinics, Kansas City; Pharmacy and Pediatric Pharmacotherapy; Mentors: Kathleen Neville, M.D., M.S.; Mark Connelly, Ph.D.

- Title: "Normative Pupillometry in Pediatrics"

- Rationale for study: Pupillometry can be used to determine analgesic response in patients who might otherwise not be able to communicate their pain level, such as postoperative, nonverbal, and pediatric patients. Newer technology is available that has simplified the acquisition of this data.
- Research protocol: Determining normal pupil size and reactivity in infants, children, and adolescents
  - Inclusion criteria: healthy children ages 1–17
  - Exclusion criteria: any child with a chronic illness known to affect pupil size, who is taking any medication known to affect pupil size, and/or who is unwilling or unable to participate.
- Methodological issues:
  - Operator training to ensure consistent measurements
  - Verbal assent from the parent or guardian and from the patient if 7 years or older
  - Instrument output: maximum/minimum pupil size and constriction/dilation velocity
  - Enrollment locations: outpatient clinics and private clinics
- Preliminary results:
  - 91 patients enrolled to date, evenly split by gender and racial distribution consistent with what is seen at the institution
  - Data analyzed for 85 patients
  - Maximum pupil size: 20 percent correlation with age; minimum pupil size: 9 percent (statistically significant)
- Plan for completion:
  - Analyze size/reactivity data when enrollment reaches 50 percent.
  - Finish enrollment in first quarter of 2013.
  - Explore additional factors of variability in observed pupil size and reactivity.

Jennifer Goldman, M.D.; Children's Mercy Hospitals and Clinics, Kansas City; Pediatrics and Infectious Diseases; Mentors: J. Steven Leeder, Pharm.D., Ph.D., Leon Van Haandel, Ph.D., Robin Pearce, Ph.D., Andrea Gaedigk, M.D., Ph.D.

- Title: "Variation of Bioactivation and Detoxification of Trimethoprim in Children
- Rationale for study:
  - Increased use of trimethoprim-sulfamethoxazole (TMP-SMX) for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) skin/soft tissue infections
  - Increased use in TMP-SMX resulted in adverse drug reactions in children
  - Historically, sulfamethoxazole implicated in adverse drug reactions
- Research protocol:
  - Aim #1: Determine whether TMP reactive metabolites formed *in vitro* can be identified *in vivo*
  - Aim #2: Characterize the metabolic pathways responsible for reactive metabolite formation
  - Aim #3: Evaluate the impact of genetic variation in drug biotransformation pathways on the total burden of reactive metabolites
  - Proof of concept study
- Methodological issues:

  - *In vitro:* human liver microsomes to identify biotransformation metabolic pathways using physiologic concentrations of TMP-SMX
  - *In vivo:* human urine metabolites to identify potential reactive metabolites and characterize population variability
  - *In vivo:* genotyping of drug metabolizing enzymes in patients
  - Enrolling 20 children, ages 2–17, who are on TMP-SMX and tolerating it
  - Collecting urine and saliva or blood to do the genotyping
- Preliminary results: Reactive metabolites of TMP-SMX detected *in vivo*
- Plan for completion:
  - Enrollment: August 20, 2012–December 2012
  - Analysis of urine metabolites: ongoing
  - Genotyping of metabolizing enzyme: at completion of enrollment, pending *in vitro* microsome results
  - Future direction: Identify the burden of reactive metabolites relative to stable metabolites related to enzyme expression in children presenting with TMP-SMX adverse drug reactions to predict those who are at highest risk for developing adverse drug reactions to TMP-SMX.

Dawn Pinchasik, M.D.; Cincinnati Children's Hospital Medical Center; Hematology and Oncology; Mentors: Maureen O'Brien, M.D., Alexander Vinks, Pharm.D., Ph.D.

- Title: "Predictors of Delayed Methotrexate Clearance During High-Dose Therapy"
- Rationale for study:
  - High-dose methotrexate (MTX) is used to treat several pediatric malignancies.
  - Numerous toxicities have been described.
  - Toxicities increase with exposure.
  - Plasma MTX concentrations are carefully monitored as an estimate of clearance.
  - Delayed clearance is not a rare complication. It may occur early on or present after an initial period of apparently normal clearance.
- Research protocol:
  - To determine clinical predictors of delayed MTX clearance following high-dose therapy
  - To develop a PK model of delayed MTX clearance
  - To identify pharmacogenetic polymorphisms that may be associated with terminal delays in MTX clearance
- Methodological issues:
  - Identified 60 patients treated with MTX from January 2010–January 2012 who have complete electronic medical records.
  - Many have germline DNA stored in repository.
  - PK modeling will be done using MW/Pharm and additional data analysis will be done using SAS software.
- Preliminary results:
  - Able to identify 59 total patients: 32 with acute lymphoblastic leukemia (ALL); 16 with osteosarcoma (OS); 13 non-Hodgkin lymphoma (NHL).
  - One-third did not clear their MTX as predicted.
- Plan for completion:
  - Data collection in process

- Anticipate beginning data analysis in January 2013
- Currently seeking funds for pharmacogenetic studies
- Manuscript anticipated ready by July 2013.

Andrea Hahn, M.D.; Cincinnati Children's Hospital Medical Center; Infectious Diseases and Pharmacology; Mentors: Robert Frenck, M.D., Alexander Vinks, Pharm.D., Ph.D.

- Title: "Pharmacogenomics of β-lactam Associated Neutropenia"
- Rationale for study:
  - β-lactam antibiotics represent 60 percent of antibiotics prescribed in the United States; 15 percent will develop a reversible neutropenia with prolonged therapy.
  - The study will look at multidrug resistance protein 4 (MRP4) present in renal and bone marrow cells and at organic anion transporter (OAT) in renal cells.
  - Different single nucleotide polymorphisms (SNPs) have been shown to affect *in vitro* protein function and individual drug response.
- Research protocol:
  - Objectives: To identify whether SNPs in MRP4 or OAT and the PK of β-lactams are associated with neutropenia
  - Retrospective case/control study design: cases (n=100) and controls (n=150) genotyped for 10 SNPs likely to affect protein function; PK studies in subjects receiving β-lactams at time of enrollment
  - Data analysis: logistic regression analysis to generate odds ratio; genotype (independent variable) versus neutropenia (dependent variable) to see if there are increased odds with either the serum levels of β-lactams, the SNPs present in MRP4, or the SNPs present in OAT
- Methodological issues:
  - A problem would be finding a significant SNP not associated with neutropenia. To address this, covariates in logistic regression analysis include gender, race, and ethnicity.
  - Since there might be another common cause for neutropenia, the study will exclude those with a history of a prior non-medication associated neutropenic episode or concurrent medications that are highly associated with development of neutropenia, and the covariates in logistic regression analysis include age, antibiotic class, and duration of antibiotic therapy.
- Preliminary results: The study has been institutional review board (IRB) approved and will begin recruiting subjects soon.
- Plan for completion:
  - Screening and enrollment: March 2014
  - Clinical trial: May 2014
  - Data analysis: July 2014
  - Manuscript: September 2014.

Jason Wiles, M.D.; Cincinnati Children's Hospital Medical Center; Neonatalogy and Clinical Pharmacology; Mentors: Henry Akinbi, M.D., Alexander Vinks, Pharm.D., Ph.D.

- Title: "Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome"
- Rationale for study:
  - Neonatal Abstinence Syndrome (NAS): Chronic *in utero* exposure to opiates is a major public health issue. There is substantial variability in the treatment modalities of infants who experience opiate withdrawal (morphine, methadone, buprenorphine, etc.), and few PK studies are available to guide drug choice or dosing strategies.
  - Pertinent ongoing NIH studies include J. Van Den Anker, et al. (Children's National) and W. Kraft, et al. (Thomas Jefferson).
- Research protocol: The study objective is (1) to construct a PK model of methadone in neonates using MW/Pharm software and (2) to validate this model in infants admitted to the neonatal intensive care unit (NICU) for pharmacologic therapy of NAS.
- Methodological issues:
  - D-optimal sparse sampling design
  - Three to four samples from each infant
  - Blood samples collected on Guthrie cards
  - LC-MS/MS to determine blood concentration of methadone
  - PK analysis by non-linear mixed effects modeling (NONMEM)
  - Individual Bayesian PK parameter estimates using MW/Pharm software
  - Associations between demographic and PK parameters using SAS software
- Preliminary results:
  - PK model suggests that starting dose for methadone may be unnecessarily high.
  - Study has obtained IRB approval.
  - Researcher plans to proceed with the validation study as described.
- Plan for completion:
  - Based on the incidence of NAS at Cincinnati Children's, there is sufficient patient enrollment to conclude the study anticipated in approximately 1 year.
  - Anticipate data analysis in fall/winter 2013.
  - Plan for manuscript completion and submission for publication spring 2014.

Kevin Downes, M.D.; Cincinnati Children's Hospital Medical Center; Mentors: Stuart Goldstein, M.D., Alexander Vinks, Pharm.D. (*presentation given by Dr. Vinks in Dr. Downes' absence)*

- Title: "Biomarkers for AKI in CF"
- Rationale for study:
  - Acute kidney injury (AKI) due to aminoglycoside (AG) use is common (24–30 percent among noncritically ill children beyond 5 days).
  - Prolonged and frequent AG exposure in cystic fibrosis (CF) may lead to long-term kidney damage.
  - Serum creatinine (SCr) measurement is not sensitive and underestimates cellular damage during AG use.
  - We have the ability to measure novel urinary biomarkers for AKI through the CCHMC Biomarker Laboratory including NGAL (neutrophil gelatinase-associated lipocalin), KIM-1 (kidney injury molecule-1), IL-18 (interleukin-18), L-FABP (liver-type fatty acid binding protein), and RBP (retinol binding protein).

- Research protocol:
  - Determine whether proximal renal tubular AKI urinary biomarkers detect AKI 48 hours prior to a rise in SCr by examining the relationship between clinical factors (CF-related diabetes, recent AG exposure, concomitant nephrotoxin use), and biomarker concentrations.
  - Determine whether baseline or changes in biomarkers can predict subsequent alterations in renal AG handling based on changes in PK parameter estimates (AUC, clearance) by estimating and assessing individual PK parameter estimates with a population model-based Bayesian algorithm.
  - Measure urinary biomarkers and SCr daily and serum tobramycin every 3 days.
  - Study population consists of CF patients receiving once-daily IV tobramycin for a pulmonary exacerbation.
  - Analysis conducted using ROC curves for each day of the study; determine test characteristics of each biomarker at different cutoffs.
- Methodological issues:
  - Small population: Enroll 60 patients over 18 months.
  - Hawthorne effect: Change in behaviors (by inpatient medical team) because of being involved in study may decrease AKI rate.
  - Tests will be performed as part of routine patient care: Tobramycin measurements will only be used if samples obtained within 12 hours of a tobramycin dose.
- Preliminary results:
  - Over an 8-month period, 21 percent of aminoglycoside courses were associated with AKI in CF patients.
  - Urinary biomarkers have been validated at Cincinnati Children's and others to be associated with early detection of AKI in a variety of clinical scenarios (cardiac bypass, contrast-induced nephropathy, critical illness); these have not been studied over the course of aminoglycoside therapy in children or CF patients.
- Plan for completion:
  - Enrollment: October 1, 2012–March 31, 2014
  - Biomarker measurements in CCHMC Biomarker Laboratory
  - Collaboration from Divisions of Nephrology, Pulmonology, Infectious Diseases, & Clinical Pharmacology.

Avinash Patil, M.D.; Duke University Medical Center; Mentors: Chad Grotegut, M.D., Geeta Swamy, M.D., Amy Murtha, M.D.

- Title: "Effect of Proposed Fetal Metabolites of Progesterone on Spontaneous Uterine Contractility
- Rationale for study:
  - Preterm birth is the second-leading cause of neonatal mortality in the United States.
  - Progesterone (P4) is an endogenous steroid hormone that promotes uterine quiescence.
  - Cytochrome P450 3A7 is unique to the fetal liver and may produce novel metabolites in the pregnant female.
  - Central hypothesis: Fetal metabolites of P4 exert local effects on spontaneous uterine contractility that may provide insight into innate mechanisms of uterine quiescence.

- Research protocol:
  - *Ex vivo* model of spontaneous uterine contractility using murine uterine horns from nonpregnant mice; contractility patterns are measured using a force transducer.
  - Treatments: (1) 4-pregnen-6β,17-diol-3,20-dione; (2) 16α-hydroxyprogesterone; (3) progesterone; (4) 17-hydroxyprogesterone caproate (negative control); and (5) ethanol (vehicle); treatments added in increasing concentrations.
  - Viability of the tissues verified by treatment with potassium chloride.
- Methodological issues—Endpoints:
  - Area under the effect curve (AUEC) calculated for the effect of each drug at varying concentrations on spontaneous contractility and in comparison to matched vehicle control to determine the true effect of the drug.
  - Half-maximal inhibitory concentration (IC_{50}) calculated for each candidate metabolite and control.
  - Maximal inhibitory concentration (C_{max}) calculated for each candidate metabolite and control.
- Preliminary results:
  - There was dose-dependent inhibition of spontaneous uterine contractions.
  - P4 produced greater inhibition than vehicle at 10^{-6}M ($p=0.006$; $n=6$).
- Plan for completion:
  - Complete contractility experiments with remaining treatment groups: 4-pregnen-6β,17-diol-3,20-dione; 16α-hydroxyprogesterone; and 17-hydroxyprogesterone caproate.
  - Future directions: Study the impact of P4 metabolites on oxytocin-induced uterine contractility, mechanisms underlying non-genomic effect of P4 metabolites, and genomic effects of P4 metabolites.

Mario Sampson, Pharm.D.; Duke Clinical Research Institute; Clinical Pharmacy and Pharmacokinetics; Mentors: Michael Cohen-Walkowiez, M.D., Ph.D., Danny Benjamin, M.D., Ph.D., M.P.H., Kim Brouwer, Pharm.D., Ph.D.

- Title: "Pharmacokinetics of Metronidazole in Preterm Infants: Validation of Dried Blood Spot Sampling" (completed study)
- Rationale for study:
  - In preterm infants, intra-abdominal infections are deadly.
  - These infections are polymicrobial, including anaerobes.
  - Metronidazole has excellent anti-anaerobic activity.
  - PK data for metronidazole in preterm infants are limited.
  - Metronidazole is metabolized by the liver.
  - Drug metabolizing enzyme activity increases with development.
  - Blood volume is a limiting factor for studies in neonates.
  - Dried blood spot sampling requires 1/10th the blood volume versus plasma.
- Research protocol:
  - Multicenter (N=3), open-label, PK study
  - Population (N=24): gestational age at birth <32 weeks, postnatal age <91 days, suspected serious infection
  - Intravenous loading dose of 15 mg/kg, maintenance dose of 7.5 mg/kg every 12–24 hours for 5 days

  - Sampling collected after the first dose and after multiple dosing; paired plasma and dried blood spots collected, if possible
  - Population PK analysis using NONMEM software; plasma and dried blood spot samples analyzed separately
  - Plasma and dried blood spot paired concentrations analyzed by linear regression
- Methodological issues: Weight and postnatal age were the main drivers for clearance; weight was the main driver for volume; bootstrapping was used to evaluate precision.
- Conclusions:
  - Metronidazole clearance increased with postnatal age.
  - Clearance finding expected with development.
  - The bias in population clearance and volume parameter estimates was <10 percent using dried blood spots.
  - Dried blood spot sampling can be used to evaluate metronidazole PK.

Kevin Turner, M.D., M.M.C.i.; UNC Department of Pediatrics; Duke Clinical Research Institute; Pediatrics and Informatics; Mentors Matthew Laughon, M.D., M.P.H., Danny Benjamin, M.D., Ph.D., M.P.H., Kim Brouwer, Pharm.D., Ph.D.

- Title: "Pediatric Obesity Drug Dosing Calculator"
- Rationale for study:
  - Obesity is increasing in children—prevalence has increased from 5 percent to 17 percent in 20 years; there are 12.5 million obese children in the United States.
  - Drug dosages for children are often weight-based—there is limited information on how to dose drugs in obese children.
- Research protocol:
  - Design a Web-based calculator for dosing recommendations for obese children.
  - Step 1. Ideal Body Weight Calculator: (1) User enters patient demographic data; (2) calculator references appropriate CDC growth curve; (3) calculator computes the ideal body weight; (4) calculator alerts user to the degree of obesity.
  - Step 2. Output Generator: Appropriate dosage generated by internal algorithm; algorithm is based on literature.
- Methodological issues:
  - Very few drugs have pediatric obesity dosing recommendations; the calculator structure is in place to incorporate new evidence.
  - Calculator stores two values for weights: ideal body weight and actual body weight.
- Preliminary results: The calculator provides the ideal body weight and the available information for that drug.
- Plan for completion:
  - Expand calculator to incorporate Body Surface Area.
  - Incorporate calculator into ongoing Web-based database of pediatric obesity PK data.

Kevin Watt, M.D.; Duke Clinical Research Institute; UNC Eshelman School of Pharmacy; Critical Care; Mentors: Danny Benjamin, M.D., Ph.D., M.P.H., Kim Brouwer, Pharm.D., Ph.D.

- Title: "Safety and PK of Fluconazole in Children on ECMO"
- Rationale for study:

  - Infants on extracorporeal membrane oxygenation (ECMO) are at high risk for infections.
  - *Candida* species are a common pathogen in this population.
  - Treatment of *Candida* is challenging on ECMO.
  - This population may benefit from prophylaxis but the appropriate dose is unknown.
  - This study is a PK/PD trial to determine appropriate dosing.
- Research protocol:
  - Infants were given weekly fluconazole 25 mg/kg unless on fluconazole per standard of care.
  - PK samples were drawn pre-oxygenator and from the patient at scheduled times around the first and second doses.
  - PK Analysis was conducted with the 1-Compartment Model using WinNonlin.
- Preliminary results:
  - 78 percent (7/9) were above MIC for 50 percent of the dosing interval.
  - Infants on ECMO had higher V and similar CL compared to critically ill infants not on ECMO.
  - Higher volume of distribution led to lower fluconazole exposure.
  - The appropriate dose of fluconazole for prophylaxis appears to be 25 mg/kg weekly.
  - Higher fluconazole doses (30–50 mg/kg load) are likely needed to achieve appropriate exposure.
- Plan for completion: Submitted a K23 application in June 2012 for "Physiologically Based Pharmacokinetics in Critically Ill Children."
  - Aim 1: Evaluate the ECMO circuit extraction of six commonly used antifungal drugs *ex vivo*.
  - Aim 2: Develop physiologically based pharmacokinetic (PBPK) models of fluconazole and micafungin in critically ill children.
  - Aim 3: Develop and prospectively validate through clinical trials PBPK models of fluconazole and micafungin in children on ECMO.

Tonia Gardner, M.D.; Pediatric Pulmonology, Pediatric ClinPharm; Riley Hospital for Children; Mentor: Jamie Renbarger, M.D.

- Title: "Aminoglycoside Nephrotoxicity in Pediatric Cystic Fibrosis Patients"
- Rationale for study:
  - Aggressive treatment of P. *aeruginosa* lung infections with aminoglycosides (AGs) in CF has greatly improved overall survival but results in acute and chronic toxicities.
  - There is persistent trouble despite improved therapeutic drug monitoring and shift to q24-hour dosing.
  - Acute renal failure incidence is 4.6–10.1 cases/10,000 CF patients/year, which represents approximately 100 times the general pediatric population.
  - Chronic kidney disease prevalence in CF adults is 31–42 percent.
- Research protocol:
  - Evaluate clinical risk factors associated with increased nephrotoxicity in pediatric CF patients receiving AGs.
  - Evaluate relationship between focused panel of genetic polymorphisms related to drug deposition and AG transport and increased nephrotoxicity in the same patient population.

  - Develop a pharmacologic model for prediction of risk of AG-associated nephrotoxicity using combination of clinical and pharmacogenomic factors.
- Methodological issues:
  - Retrospective data collection involves a large time investment, and information on previous courses prior to electronic medical records or via home IVs is not available, nor is information about concurrent OTC medications.
  - Creatinine is an unreliable measure of renal function in CF patients.
  - It is a challenge to obtain enough patients to detect differences in SNPs.
- Preliminary results: There was a significant difference in the percentage that had developed cystic fibrosis-related diabetes (CFRD), and significant differences in BMI, the number of antibiotic courses, and the number of patients receiving co-administered vancomycin.
- Plan for completion:
  - Continue retrospective data collection
  - Addition of CF Registry data
  - Whole blood samples currently being collected and biobanked (~85 patients thus far)
  - Megalin and cubulin SNP literature review
  - Focused DMET chip in progress (50–100 genes).

Troy Quigg, D.O.; Indiana University School of Medicine; Riley Hospital for Children; Mentors: Jamie Renberger, M.D., W. Scott Goebel, M.D., Ph.D., Todd Skaar, Ph.D., David Flockhart, M.D., Ph.D.

- Title: "Indoleamine 2,3-dioxygenase (IDO) in Allogeneic Tolerance and Graft-Versus-Host Disease (GVHD)
- Research protocol:
  - Objective: To provide prospective pilot *in vivo* data on IDO activity in allogeneic HSCT and determine the extent to which IDO activity correlates with GVHD.
  - Pilot, n = 22 evaluable (enrollment completed 12/2011)
  - Serial sampling of PBMCs, plasma—12 time points each, pre-hematopoietic stem cell transplant (HSCT) to 1-year post-HSCT; PBMCs for IDO mRNA expression analyses; plasma measurement of tryptophan and kynurenine by HPLC (Kyn/Trp ratio)
  - IDO pharmacogenomics—5mL whole blood at baseline and day +100 for SNP analyses
- Methodological issues:
  - No significant *in vivo* human IDO HSCT data had been previously published; this is meant to be a pilot to capture natural activity of IDO over time in allogeneic HSCT recipients, with a protocol designed for scheduled sampling over the course of 1 year.
  - Heterogeneous patient population to complete accrual quickly. Patients had both malignant and nonmalignant diseases, some patients had reduced intensity treatment and some myeloablative conditioning, this included both children and adults, and this was a small sample size.
- Preliminary results: Overall, the group with the GVHD ranks significantly higher compared to the IDO activity in the non-GVHD group.
- Plan for completion:
  - All sampling to be completed by 12/2012 (or sooner)
  - Abstract submission—ASBMT/CIBMTR Tandem Meetings (2/2013, Salt Lake City, Utah); Plasma data and clinical correlates

- IDO mRNA expression studies and SNP analyses through institutional funding; completion fall/winter 2012–2013.

Erin Hurley, Ph.D.; Pediatrics; The Mayo Clinic; Mentors: Jan vanDeursen and Richard Weinshilboum

- Title: "Effect of AZD1152 on BUBR1 Hypomorphism"
- Rationale for study:
  - Mosaic variegated aneuploidy (MVA) is a rare genetic disease.
  - Patients have microcephaly, growth and mental retardation, high rates of cancer, and a short lifespan.
  - MVA is caused by reduction in levels of the mitotic protein BubR1.
  - Decreased BubR1 is thought to lead to hyperactivation of AuroraB, which is important for spindle attachment.
  - Therefore normalization of AuroraB activity by inhibition with AZD1152 (Barasertib) in BubR1 hypomorphic mice may lead to reduction in MVA phenotypes.
- Research protocol:
  - BubR1 hypomorphic mice—a model system for MVA
  - Injection 6µg/g AZD1152 or 0.3M Tris starting at 7 days of age
  - Monitor for MVA symptoms, including weight, cataract formation, and onset of kyphosis
  - Examine activity levels on treadmill and in activity chambers
- Preliminary results:
  - No differences in timing to or incidence of MVA phenotypes, including weight, cataract formation, time to kyphosis, exercisability or activity (rearing, ambulation)
  - Significant increase in lifespan
- Plan for completion—Exploring whether AZD1152 may affect cardiac function:
  - BubR1 mice are prone to sudden death, which has been attributed to heart-related issues.
  - Mice are being examined by echocardiography to determine whether cardiac function is improved with treatment.
  - If cardiac function is improved with AZD1152, will examine the molecular mechanism behind this improvement.
  - If cardiac function is not altered, will examine other possibilities for lifespan increase.

Ami Desai, M.D.; Pediatric Hematology/Oncology; CHOP; Mentors: Richard Aplenc, M.D., Ph.D., Rochelle Bagatell, M.D., Sean Hennessy, Pharm.D., Ph.D.

- Title: "Neuropathic Pain Management in High-Risk Neuroblastoma Patients Receiving Immunotherapy"
- Rationale for study:
  - Neuroblastoma is a childhood embryonal tumor that arises within tissues of neural crest origin.
  - High-risk neuroblastoma: Poor event-free survival (EFS) despite multimodal therapy.
  - Yu, et al. *NEJM* 2010: Phase III RCT Immunotherapy v. Isotretinoin—showed that immunotherapy is superior to isotretinoin in EFS and overall survival in the maintenance phase of therapy.
  - Immunotherapy: Chimeric monoclonal antibody: Anti-G_{D2} antibody (ch 14.18); Cytokines: sargramostim (GM-CSF), (interleukin 2) IL-2.

  - Ch 14.18 targets the ganglioside G_{D2} present on neuroblastoma cells and pain fibers.
  - 52 percent of patients in the phase 3 RCT who received ch 14.18 had severe pain.
  - Guidelines for opioid management: morphine PCA (intravenous); gabapentin use is optional.
  - Use of gabapentin: seizures and neuropathic pain; mechanism of action; reversal of allodynia in rats injected with anti-G_{D2} antibody.
- Research objectives:
  - To validate a high-risk neuroblastoma cohort assembled using a specified algorithm in the Pediatric Health Information System (PHIS) database
  - To determine the prevalence of gabapentin use during cycle 1 of immunotherapy in patients with high-risk neuroblastoma identified in PHIS
  - To determine whether the use of gabapentin decreases pain control failure in high-risk neuroblastoma patients identified in the PHIS database receiving immunotherapy
- Study design:
  - Retrospective cohort study conducted within the PHIS, a comparative pediatric administrative data base of 43 not-for-profit, tertiary children's hospitals associated with the Child Health Corporation (CHCA)
  - Population: Patients with high-risk neuroblastoma identified in the PHIS database
  - Exposed patients: gabapentin on day 0 in cycle 1
  - Unexposed patients: no gabapentin on day 0 in cycle 1
  - Primary outcome: pain control failure (intravenous opioid use >5 days)
  - Covariates: demographics: age, gender, race, insurance status, hospital, prior opiate exposure, prior gabapentin exposure
  - Analysis including (1) χ 2 test for association between gabapentin use on day 0/cycle 1 (exposure) and pain control failure (outcome); (2) multivariable logistic regression to adjust for covariates
  - Secondary analysis of other definitions of failure: (1) escalation of care (lorazepam, midazolam, ketamine, lidocaine); (2) intravenous opioid use >6 days; (3) intravenous opioid use >6 days or escalation of care (lorazepam, midazolam, ketamine, lidocaine)
- Methodological issues:
  - Single institution validation
  - Accuracy and completeness of data can be affected because the PHIS pharmacy data reflects gabapentin and opioids that were billed for and dispensed but the administration status is unknown, no doses or time of administration of medications are known, and because of the dependence on data entry by each institution.
  - Confounding factors are due to indication, provider/institution practices, extended infusion time, and indications for opioid use.
- Preliminary results:
  - Assembling high-risk neuroblastoma cohort built from the PHIS Database using ICD-9 codes, exclusion criteria, and chemotherapy pattern review
  - Validation of cohort
- Plan for completion:
  - Summer and fall 2012: data collection, validation of the cohort, and data cleaning
  - Winter and spring 2013: data analysis
  - Spring 2013: manuscript preparation.

Jason Freedman, M.D.; Pediatric Oncology; CHOP; Mentor: Chris Feudtner, M.D., Ph.D., M.P.H.

- Title: "Antiemetic Failure in Pediatric Oncology"
- Rationale for study:
  - Chemotherapy-induced nausea and vomiting (CINV) remains a significant challenge in pediatric oncology. Some studies suggest up to 80 percent of families report this as the most distressing symptom.
  - Limited data exist on comparative effectiveness and longitudinal use of such agents in pediatrics.
  - Antiemetic failure refers to a point in therapy requiring therapeutic alteration to control CINV, such as a change of baseline antiemetic, addition of adjunctive medication, or dose alteration of already-prescribed medication.
  - Pattern, timing, and rates of failure are not well-defined.
- Research objectives:
  - To describe the patterns of antiemetic failure over multiple chemotherapy cycles in pediatric patients undergoing treatment for cancer
  - To determine whether the rate of antiemetic failure increases as the number of chemotherapy-exposed days increases
  - To determine whether rates and patterns of antiemetic failure over time differ based on the initial antiemetic regimen patients received at the start of chemotherapy
- Study design:
  - Design: retrospective cohort study
  - Source cohort: PHIS of pediatric patients with acute myeloid leukemia (AML) or OS who have received 3+ cycles of emetogenic chemotherapy; patients having received radiation or bone marrow transplantation were excluded
  - Analysis: descriptive statistics, cox regression, multivariable regression
- Validation of outcome
  - Chart review at CHOP
  - Patients with AML and OS
  - Determine positive predictive value and negative predictive value of therapeutic alteration in database as indicator of antiemetic failure in hospital patient record
- Methodological issues:
  - Retrospective observational study.
  - Limits of database include therapeutic alteration as a surrogate for antiemetic failure; billable charge as receipt of medication is not reliable; no dosage information; only inpatient data.
  - Bias.
  - Potential confounders such as age and sex need to be controlled for.
  - Practice variation at multiple hospitals can potentially influence the findings.
- Preliminary results: Project in progress
- Plan for completion:
  - Summer 2012: IRB amendments for validation
  - Fall 2012: data abstraction and cleaning, data analysis, and validation study
  - Spring 2013: finish data analysis; manuscript preparation

- July 2013: completion of project.

M. Elena Rodriguez, MS.P., M.D.; Pulmonology; Nemours AIDHC; Thomas Jefferson University; Mentors: Thomas H. Shaffer, MS.E., Ph.D., Scott Waldman, M.D., Ph.D.

- Title: "Translational Animal Model of Asthma"
- Rationale for study:
  - Cryptorchidism, or undescended testis (UDT), is one of the most common male congenital anomalies—incidence: 3 percent full-term versus 30 percent premature; overall 1 percent.
  - Reflects gene-environment interactions.
  - Case-control study: UDT patients have greater incidence of asthma.
  - The ORL rat is a Long Evans substrain with inherited UDT.
  - Respiratory distress and wheezing in observed in ORL rats.
- Research protocol:
  - Wild-type (WT) rats (n = 9); 108 ± 6 g weight.
  - ORL rats (n = 14); 95 ± 23 g weight.
  - 4 weeks of age: equivalent to early puberty/late childhood.
  - BL respiratory mechanics: resistance (RI), compliance (Cdyn).
  - Methacholine (MCh) challenge response (0.3 to 12.5 mg/ml).
  - Biomarkers of lung inflammation (IL-4, IL-6, TNF-α).
  - Null hypothesis: ORL and WT rats are equivalent in response to MCh challenge and expression of inflammatory biomarkers in lung.
- Methods:
  - Anesthesia: ketamine and xylazine IP
  - Ventilated through tracheal cannulae
  - Acclimation (10 min) to stabilize inside plethysmography chamber
  - Respiratory mechanics and vital signs at rest, baseline, and q 5 min. during MCh administration
  - Euthanasia with Euthasol, thoracotomy, tissue harvesting
- Preliminary results:
  - ORL rats compared with WT rats are significantly more responsive to MCh challenge.
  - ORL rats have lower lung expression of IL-6 and IL-4.
- Future goal: To completely profile this animal model and test therapeutic options guided by pathophysiology/genetic profiles.
  - Histomorphometry of lungs and diaphragm
  - Transcriptomic analyses of lung and diaphragm
  - Correlate lung function, inflammatory biomarkers, histomorphometry, and transcriptomic analyses to define mechanism-based therapeutic targets.

Kara Calkins, M.D.; Neonatology; University of California, Los Angeles (UCLA); Mentors: Sherin Devaskar, Stephen Shew, James Dunn, M.D., Robert Venick

- Title: "Prospective, Case-Controlled Trial of 24 Weeks of Intravenous Fish Oil in Children With Parenteral Nutrition-Associated Liver Disease"
- Rationale for study:

  - Parenteral nutrition (PN) maintains hydration and electrolyte balance and promotes growth when enteral nutrition is not possible.
  - Intravenous soybean oil (SO) is often prescribed with PN and has been linked to the development and progression of Parenteral Nutrition Associated Liver Disease (PNALD).
  - Cohort studies have reported that intravenous fish oil (FO) biochemically reverses cholestasis.
- Research protocol: FO and SO cohorts
  - Efficacy: To determine whether FO will effectively reverse PNALD when compared to SO, by conducting serial liver function tests, measuring triglyceride and albumin concentrations, and taking platelet counts
  - Safety: To determine whether FO safely reverses PNALD when compared to SO, by measuring serial INRs, triene-tetraene ratios, and growth
  - Mechanism of action: To determine how FO alters fatty acids and inflammatory proteins and genes, by measuring serial plasma and RBC fatty acids, TNF-α, IL-6, and microarrays
- Preliminary results: Resolution of cholestasis, defined as direct bilirubin less than 2 on two consecutive occasions: 17 percent of the FO cohort achieved resolution, while only 5 percent of the SO achieved resolution.
- Methodological issues:
  - Use of historical controls—matched 2:1 on gestational age and GI diagnosis
  - Difference in not only composition, but also dose of FO and SO—regression analysis takes this into account
  - Use of plasma and red blood cells (RBCs) rather than liver tissue, but in process of obtaining IRB approval for hepatic tissue
- Plan for completion:
  - Continue enrollment
  - Continue to build repository
  - Perform translational studies.

Kellie Lim, M.D.; UCLA; Mentors: Marck Riedl, M.D., M.S., Maria Garcia-Lloret, M.D., Samuel Wald, M.D.

- Title: "Propofol Use in the Egg-Allergic Pediatric Population"
- Rationale for study:
  - Prevalence of food allergies is increasing.
  - Drugs with food-based vehicles are contraindicated in those with specific food allergies.
  - Propofol contains egg yolk lecithin, but is unlikely to cause anaphylaxis in egg-allergic patients.
  - Lecithin is not a known egg allergen.
  - Propofol causes anaphylaxis in 1 of 45,000 doses and severe adverse events in 1 of 15,000 doses.
  - Quick onset and offset of action, so it is the preferred sedative in many procedures.
- Research protocol:
  - Establish the frequency of type 1 hypersensitivity reactions in egg-allergic patients challenged with propofol by performing a skin prick and intradermal testing to propofol with controls (saline and histamine). If negative to propofol, subject to undergo propofol

challenge at 20 mcg/kg via IV push. If no adverse reactions, subject to receive propofol for sedation while undergoing procedure.
  - Determine sensitivity and specificity of immediate hypersensitivity skin prick testing to propofol and egg yolk lecithin in egg-allergic patients by performing an immediate hypersensitivity skin prick testing to propofol and egg yolk lecithin along with controls (saline, histamine) in egg-allergic subjects.
- Methodological issues:
  - Sensitivity to propofol may not equate to actual allergy; it would be dangerous to have sensitized subjects undergo propofol challenge.
  - Propofol may be contaminated with egg allergens.
- Preliminary results:
  - Recruited one subject for skin testing to propofol and egg yolk lecithin; subject negative to both, but positive to egg yolk and egg white.
  - Recruitment of one subject for propofol challenge in process.
- Plan for completion:
  - Recruitment of at least 20 subjects for each study aim.
  - Will expand study population by allowing referrals from physicians in addition to direct recruitment.

Neha Vaghasia, M.D.; Pediatric Hematology/Oncology: UCLA T32 ICPTP and K30 Program; Mentors: Chris Denny, M.D., Noah Federman, M.D.

- Title: "Targeting Liposomes Toward Novel Pediatric Osteosarcoma Therapeutics"
- Rationale for study:
  - OS is the most common primary bone malignancy in children and adolescents.
  - Trends in 5-year-survival rates over the past several decades have minimally improved.
  - Side effects on normal cells are primarily responsible for significant and dose-limiting toxicities.
  - Nanoparticles represent a promising new technology for application to pediatric malignancies.
  - A nanosized vehicle specifically targeting OS would allow delivery of increased amounts of cytotoxic therapies to tumor cells while sparing normal tissue.
  - Activated leukocyte cell adhesion molecule (ALCAM) or CD166 is a type I membrane glycoprotein and a member of the immunoglobulin superfamily.
  - It was recently found that ALCAM is highly expressed in a panel of bone cancer cell lines derived from patients with OS.
- Research proposal:
  - To develop a novel anti-ALCAM targeted nanoparticle that could deliver cytotoxic agents specifically to OS cancer cells to achieve improved cell kill while minimizing the bystander effects to normal cells.
  - Treatment is initiated at a tumor volume of 300 mm3 and will consist of two injections, on day 1 and day 8.
  - Bioluminescence imaging will be used to assay *in vivo* response.
  - All mice will be euthanized at a tumor volume of 1.5cm3.
  - Tumors will be harvested from the mice for sectioning and TUNEL staining.

  - Mouse organs will be harvested for fluorescent microscopic evaluation of nanoparticle deposition and toxicity.
- Preliminary results: Tumors in the first group grew at a slower rate.
- Plan for completion:
  - Goal for statistical significance n=80.
  - Develop a novel anti-ALCAM targeted nanoparticle that could deliver cytotoxic agents specifically to OS cancer cells to achieve improved cell kill while minimizing the bystander effects to normal cells.
  - If successful, this has the potential for enormous therapeutic benefit.
  - Goal of work is ultimately to translate these novel developments to the clinic.

Arun Panigrahi, M.D.; Pediatric Hematology/Oncology; University of Chicago; T32 Clinical Pharmacology Fellow; Mentors: Eileen Dolan, Ph.D., John Cunningham, M.D.

- Title: "Variability of Response to Hydroxyurea in Sickle Cell Disease"
- Rationale for study:
  - Amelioration of the sickle cell disease phenotype occurs with induction of fetal hemoglobin (HbF).
  - Hydroxyurea (HU) is the only licensed HbF induction agent—multifactorial mechanism and variable response; induction of leucopenia is the key clinical measure of response.
- Research protocol:
  - Lymphoblastoid cell lines assayed—CEU: 90; YR1: 87; YR3: 15; ASW: 92.
  - Cell susceptibility to growth inhibition after exposure to 0, 10, 25, 50, 100, 250, 500, and 1000 µmol/L of hydroxyurea was evaluated using an Alamar blue cytotoxicity assay.
  - This assay is performed 72 hours after treatment with HU and 24 hrs. after addition of Alamar Blue.
  - Concentrations chosen were appropriate for clinical setting.
- Methodological issues:
  - Assay performed in duplicate to generate six values per concentration
  - Data analyzed for standard deviation, plot of curve, and normality
  - IC50 calculated for each cell line and log2 transformed
  - Population measures subsequently analyzed
- Plan for completion:
  - Perform GWAS with HapMap database.
  - Evaluate markers of expression (exon array, micro RNA, protein data, methylation, etc.).
  - Consider genetic markers implicated previously in SCD severity, HbF production, and leucopenia.
  - Develop validating tissue-specific stem cell assays.

T32 Trainee Introductions

The trainees attending but not presenting were invited to introduce themselves and state their research interests:

- Benjamin Black, M.D.; Children's Mercy Hospitals and Clinics
  - Subspecialty: Clinical pharmacology fellow; developmental and behavioral pediatrics

  - Research interest: Predictors for response to ADHD medication

- Angela Etzenhouser, M.D.; Children's Mercy Hospitals and Clinics
  - Subspecialty: General pediatrician; first year in clinical pharmacology training
  - Research interest: Adverse drug reactions

- Ryan Funk, Pharm.D.; Children's Mercy Hospitals and Clinics
  - Subspecialty: Clinical pharmacology fellow
  - Research interest: Predict response to low-dose methotrexate in juvenile idiopathic arthritis

- Jonathan Wagner, D.O.; Children's Mercy Hospitals and Clinics
  - Subspecialty: Combined pediatric cardiology and clinical pharmacology fellow
  - Research interest: Cardiovascular drug research in children, specifically safety and efficacy of the clinical use of statins (HMG-CoA reductase inhibitors) in children

- Maryann Mazer, M.D., Pharm.D.; Children's National Medical Center
  - Subspecialty: Adult emergency medicine; medical toxicology; clinical pharmacology
  - Research interest: Bringing clinical pharmacology skills into toxicology, especially intravenous acetaminophen as well as drugs of abuse and emerging opiates

- Lawrence Ku, M.D.; Duke University Medical Center
  - Subspecialty: Neonatology fellow
  - Research interest: Drug metabolism in premature neonates

- Poonam Sharma, M.D.; SUNY Downstate
  - Subspecialty: Neonatology
  - Research interest: Retinopathy of prematurity

- Marianne Augustine, M.D.; CHOP
  - Subspecialty: Gastroenterology fellow; clinical epidemiology
  - Research interest: Pediatric liver transplantation, specifically withdrawal of immunosuppression

- Jennifer Wilkes, M.D.; CHOP
  - Subspecialty: Pediatric hematology/oncology; clinical pharmacoepidemiology
  - Research interest: Infectious complications in children being treated for cancer, specifically the appropriate use of antimicrobial prophylaxis

- Nicole Zane, Pharm.D.; University of North Carolina, Chapel Hill
  - Subspecialty: Third year of Ph.D. program at UNC
  - Research interest: The ontogeny of drug-metabolizing enzymes and how that affects PK in children ages 2–10 years

Day 2

Day 2 began with the fellows breaking into groups to discuss (1) the fellows' training in relation to their subspecialties and (2) how the fellows can be ambassadors for clinical pharmacology to their programs. The groups then shared their feedback.

Group A. This group spoke about potential collaborations integrating research and core strengths, platforms at different facilities, and access to patient populations and multicenter trials. The group discussed problems in pediatric clinical trials such as the limited number of participants and the need for standardization of therapy.

Group B. A useful resource would be to have a small interest group through which to e-mail, share resources, have a drop box for documents, share other files such PowerPoint presentations and lecture notes, and discuss interesting cases. The group also thought it would be beneficial to have had time for expert questions and input after the presentations on their research projects given on Day 1 of this meeting.

Group C. All the fellows in this group had a significant interest in PK, but since they are not as strong in this area would like the opportunity to collaborate, perhaps through webinars. They also thought a board review course in preparation for the clinical pharmacology boards would be useful. It would be a good idea for junior faculty to be mentors in addition to the more senior faculty members. Dr. Waldman noted that there is a board review course put on at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) meeting. He stressed that all the fellows should be going to the ASCPT and the Pediatric Academic Societies (PAS) meetings each year. Dr. Barrett mentioned that CHOP is the U.S. site for the Sheiner and Rowland Advanced Course in PKPD 5-day workshop, which will be in April 2013, and that it would be an excellent opportunity for the fellows. CHOP also conducted a 3-day workshop, with participation from industry, on modeling/simulations approaches specific to pediatrics last year and will do so again the first week of June 2013. Dr. Waldman commented that there are many venues available for the fellows to get together, and the leadership will attempt to create more opportunities, for example, at ASCPT.

Group D. This group talked about the spectrum of fetal life and how they treat the same patients but at different points. Collaboration would be helpful—what exposures the fetus has had *in utero* and how that translates into treatment the infant receives in the NICU. Concerns include polypharmacy in neonatology, trying to account for variations in practice patterns across the country, and drugs used on-label versus off-label. Knowing more about fetal exposures can come into play in terms of modernizing the Barker hypothesis—the idea that the fetal origins of adult disease can impact generations. The group discussed lactation and breast milk and that there needs to be a better understanding of the use of drugs and how they impact breast milk. Dr. Blumer noted that it is important to encourage the collaboration of the obstetricians and neonatologists.

Group E. Pulmonology, critical care, and PK were all represented in this group. Live meetings are helpful to find out what others are researching. The *PedPharmHub* appears to be an excellent

way to stay abreast of what colleagues are researching and are interested in. While there are ongoing webinars, short courses would be a good addition, and it would be nice to have individuals from such courses at meetings such as this to introduce topics to the group. The ASPCT course would be useful to ensure they are prepared for the clinical pharmacology boards. The mentorship model at the fellows' institutions is to meet with the senior faculty less frequently. For example, the model at Duke encourages frequent interaction with junior faculty, such as to prepare manuscripts with the aid of a junior faculty mentor before sending the manuscripts to the senior faculty mentor. This seems to work well. There was discussion about the limitations of travel for meetings such as this and short courses; having the option to connect online would be beneficial. Dr. Waldman noted that the *PedPharmHub* is the place where such online connections could occur, but also that face-to-face meetings are extremely important.

Introduction to the Principles of Pediatric Clinical Pharmacology Lecture Course and the Pharmacometrics Module

George Giacoia, M.D., Medical Officer, OPPB, NICHD, NIH

Dr. Giacoia presented a brief background of the purpose of the T32 programs in clinical pharmacology, noting that the reason for these programs is to address the shortage of scientists who have formal training in pediatric clinical pharmacology, which presents a major roadblock for the advancement of pediatric therapeutics. The BPCA of 2007 is legislation that mandates pediatric pharmacologists to be specifically included in existing NIH career development and loan repayment programs. The T32 training grants are funded through this BPCA legislation.

The current fellows consist of a group from the NIGMS-NICHD T32 program in adult clinical pharmacology with a pediatric component, the NICHD T32 program in pediatric clinical pharmacology, and the U54 pediatric and developmental pharmacology research centers. The T32 program in obstetric fetal pharmacology is soon to be added. There are 8 fellows from NIGMS-NICHD institutions, 11 from NICHD T32 institutions, 13 from other funding sources, 4 from a pediatric pharmacoepidemiology program, 4+ from U54 centers for developmental pharmacology, and 1 in adult clinical pharmacology. The subspecialties represented are pediatric hematology-oncology, neonatology, pediatric cardiology, drug metabolism pharmacometrics, pediatric intensive care, pediatric infectious diseases, pediatric gastroenterology, pediatric allergy-immunology, adolescent medicine, behavioral and developmental medicine, and pediatric pulmonology.

Dr. Giacoia briefly reviewed the results of the survey of the T32 fellows that asked how their time was spent:

- NIGMS-NICHD fellows (University of Chicago, Thomas Jefferson University, Mayo Clinic, UCLA, UCSF, UNC, Duke University, and Vanderbilt University): Most classes were in adult clinical pharmacology, with very few in pediatric clinical pharmacology. There was a variety in the time spent in clinical and in basic/translational research.
- Pediatric NICHD T32 fellows (Cincinnati Children's Medical Center, Indiana University, University of Missouri-Kansas City, CHOP): Most classes were in pediatric clinical pharmacology, with very few in adult clinical pharmacology. There was mostly time spent in clinical research, with very little in basic/translational research.

- Very few fellows (78%) rotated to another laboratory clinical setting.
- Most of the fellows' (89%) clinical research is related to their pediatric subspecialty.
- Most of the fellows (83%) do not participate in clinical pharmacology toxicology consultation services. Dr. Giacoia noted that this is an interesting statistic given that this consultation is a requirement of the American Board of Clinical Pharmacology.
- A majority (73%) of the fellows do not participate in case-based seminars on applied clinical pharmacology.
- Participation in grant writing was split (56% yes; 44% no), but this may not be an accurate statistic because there are both first- and second-year fellows represented in the survey.
- Post-fellowship career plans are split between practicing medicine (44%) and serving as junior faculty in clinical pharmacology or a subspecialty area (56%).
- The majority of the fellows had little (43%) to no (50%) prior experience in pharmacometrics as applied to adult clinical pharmacology.
- Individualized dosing and PK/PD modeling in children were the two most prevalent areas of interest of the fellows (both 69%).

Dr. Giacoia pointed out that adult clinical pharmacology is not recognized by the American Board of Medical Specialties (ABMS), and pediatric clinical pharmacology is not a formally recognized subspecialty of adult clinical pharmacology. Pediatric pharmacologists have adapted adult methodologies and tools to pediatrics. The NIGMS T32 postdoctoral program is a vehicle for adding a pediatric clinical pharmacology training component. The goal is not to simply occasionally train those interested in pediatric pharmacology, but rather to develop a program in pediatric clinical pharmacology and therapeutics.

The NICHD created a Core Curriculum Harmonization Committee chaired by Ralph E. Kauffman, M.D., of the University of Missouri-Kansas City School of Medicine, which has completed the first phase of its work. The Core Curriculum Harmonization Advisory Board is chaired by Russell W. Chesney, M.D., A.B., of the University of Tennessee Health Science Center and includes members from the FDA and the AAP, as well as other well-known figures in the field of clinical pharmacology.

The NICHD Core Curriculum Harmonization Committee has developed an operational definition of pediatric clinical pharmacology:

"Pediatric clinical pharmacology is a multidisciplinary translational specialty that integrates our knowledge of developmental changes during differentiation, growth, and maturation, from conception to young adulthood, with the knowledge and research tools of basic human pharmacology and applied pharmacology to develop new knowledge and optimize pharmacotherapy in the pediatric patient population."

Dr. Giacoia stressed two things regarding this definition:

1. Pediatric clinical pharmacology is multidisciplinary—interaction among the disciplines is essential in this day and age.
2. Pediatric clinical pharmacology uniquely incorporates the dimension of growth and development during infancy and childhood into an understanding of human pharmacology.

Core content can be selected from the following elements with the addition of elective courses not part of the core:

- Developmental pharmacology
- Developmental toxicology
- Developmental pharmacogenomics
- Pediatric pharmacoepidemiology
- Pharmacometrics
- Bioinformatics applications
- Pediatric drug development/regulatory science
- Pharmacology of special pediatric populations (for example, newborns, adolescents)
- Bioethics
- Laboratory-based learning
- Complementary didactic teaching and education to satisfy requirements of American Board of Clinical Pharmacology
- Career development activities
- Presenting data, grant writing and strategy, writing papers, evaluating papers for publication, career planning
- Administrative experience
- Clinical pharmacology and toxicology consultation services experience.

The 2012–2013 NICHD Principles of Pediatric Clinical Pharmacology Lecture Series will be made up of the following:

- Module 1: Pharmacometrics
- Module 2: Drug metabolism and transport
- Module 3: Assessment of drug effects
- Module 4: Pharmacotherapy
- Module 5: Drug effects and disposition in special settings
- Module 6: Pediatric drug formulations
- Research and academia.

Dr. Giacoia noted that this program will be mandatory for the T32 fellows funded by the NICHD. It will complement the NIH Clinical Center adult course in Principles of Clinical Pharmacology, with both awarding a certificate for 75 percent attendance. Both series run from September 2012 through April 2013. The adult course does not include clinical trials or drug formulations but it does include drug interactions; the pediatric course includes pediatric clinical trials and pediatric formulations but does not include drug interactions.

An educational consultant from UCLA who is an expert in curriculum development has assisted in the curriculum development and design process. Phase 1 included developing the overall goal of the curriculum, identifying and selecting main topics and subtopics, formulation of learning objectives for each main topic and subtopic, and developing and selecting content for each main topic and subtopic to match the learning objectives. This led into Phase 2, the curriculum design, which consisted of identifying specific methods of learning, determining the appropriateness of learning methods, organizing content and learning methods to link the methods to the objectives,

and finally developing a plan to evaluate the learning objectives. After April, the program format may be adjusted as necessary. Additionally, it will utilize a spiral curriculum, where students repeat the study of a subject at different levels, each time at a higher level of difficult and in greater depth.

The NICHD action plan for the 2013 fiscal year and beyond includes the following elements:

- Extension of funding period from 2 years to 5 years, matching the NIGMS parent grant award
- Annual evaluation of each program
- Implementation of a core curriculum in pediatric clinical pharmacology with mandatory fellows' participation
- This current face-to-face meeting of fellows on September 13 and 14, 2012 (mandatory participation by fellows funded by NICHD; travel expenses paid by NICHD)
- Invitation of all T32 principal investigators (PIs) and co-PIs to attend the fellows' September meeting
- Establishment of a pediatric journal club on pediatric therapeutics
- Providing fellows with training on grantsmanship (initial session July 26)
- Establishment of fellows-mentors interest groups to stimulate discussions and collaborations across different institutions
- Promotion of fellows' teaching skills (for example, development of pharmacology lectures for other subspecialists fellows)
- Interaction with attending subspecialists.

Key Elements of Pharmacometrics: What You Can and Can't Do with Pharmacometrics to Support Pediatric Research

Jeffrey Barrett, Ph.D., CHOP

The focus is on designing good experiments and good clinical trials, which fulfill study objectives, are well-powered and well-designed, collect meaningful data, collect clinically relevant doses and regimens, minimize or eliminate sources of confounding factors, and study the appropriate populations/characteristics. Pharmacometrics is a tool that can help ensure these trials are designed correctly. It can help define population-PK (pop-PK) or PK/PD, give dosing guidance and adjustments, identify first time in manner (FTIM)/FTIM(P) dose, design parameter evaluation, provide trial simulation, and predict disease progression. Critical design elements include dose selection, sample size, and sampling scheme.

Dose Selection. For dose finding, a target or endpoint is known or theorized based on adult or other data; dose-exposure is to be defined. In the more commonly used equivalence approach, exposure requirements are based on adult experience—"equivalent" safety and efficacy is assumed by matching exposures. The issue from the standpoint of the pediatric caregiver is whether the equivalence approach is good enough. Currently a simple rule for dose selection does not exist, with current rules either under-predicting across age strata, under-predicting infants and neonates, or over-predicting for children less than 1 year old.

Sample Size. The classical statistical approach to determining sample size is by a pooled variance estimate and "delta" to be detected between adjacent strata (typically FDA age strata). Clearance is typically the parameter of interest. This approach does not consider the precision in the estimation of clearance nor the fact that this test is likely different for various adjacent age groups. A simulation-based approach is reliant on a well-defined pop-PK model that projects dose-exposure over the age continuum and can simulate various sample sizes for each age stratum and assess bias and precision via replication. This approach involves randomized sampling schemes to balance design points against blood volume constraints.

Common Workflow. To evaluate doses or exposure profiles thought to yield equivalent exposures to adults, the researcher will generate PK distribution for intended age-weight subpopulations at all doses considered, compare overlap in ranges across populations and age groups, and compare with adult profiles. To estimate sample size to detect a difference in key parameters between treatment groups, adults or historical controls, the researcher would take all the steps to evaluate doses or exposure profiles in addition to deriving metrics for individual simulated subjects (for example, AUC, Cmax, CL), comparing groups via ANOVA, and find delta and variance to estimate sample size. To select a sampling scheme that will yield "meaningful" parameter estimates in children, the researcher will need to define critical time points for PK parameters based on the adult model, simulate pediatric profiles with various combinations of sampling time using pediatric-scaled model, re-fit simulated data, and compare precision and bias. The sampling scheme needs to be thought of at the beginning of the process as well. To scale across age ranges, patient-specific factors related to their care or treatment are considered.

Pharmacometrics cannot provide extrapolation outside a "reasonable" bridging strategy or realistic (untestable) assumptions, cannot salvage poorly designed trials, and cannot define covariate relationships that have not been adequately sampled. Dr. Barrett provided an example of what pharmacometrics can do with the discussion of a multicenter phase 2 labeling trial in a new pediatric population. It used historical data and a pop-PK model in children, though it involved a new disease population, and it evaluated the effect of a sample scheme and sample size per age strata on the bias and precision of key PK/PD parameters. The example of a BPCA trial on actinomycin-D (AMD)/vincristine (VCR) in children with cancer illustrated how modeling and simulation were useful in designing the trial so that it could still report meaningful results. The third example was a fluconazole study, which was a prospective PK trial to establish a pop-PK model of fluconazole disposition in infants 23–40 weeks gestation and less than 120 days, to facilitate a PK trial by leveraging clinical practice, and to determine dosage guidelines that provide adequate exposure for treatment and prevention of invasive candidiasis. From this study, it was found that a pop-PK study design can leverage routine care. Conventional wisdom can be challenged by a model that is well-predicted. All these examples illustrate that pharmacometric approaches are increasingly employed to support pediatric research and development. The adoption and use of appropriate pharmacometric techniques is a regulatory expectation for pediatric submissions. The use of appropriate pharmacometric techniques is behind many of the recent labeling changes and dosing guidance in children.

Population-PK/PD to Support Individualized Dosing Guidance for Children

Sander Vinks, Pharm.D., Ph.D. Cincinnati Children's Hospital Medical Center

Pharmacometrics can be defined as the science that uses models based on clinical pharmacology, physiology, and disease for quantitative analysis of interactions between drugs and patients. It includes pop-PK/PD modeling, exploring exposure response for drug efficacy and safety, clinical trial simulation for dose optimization, and disease-progression modeling. Modeling and simulation can describe drug PK/PD behavior; collect informative data to use as Bayesian priors for designing model-based and individualized dosing regimens; predict and therefore control the system, that is, the serum and other compartments; and change passive "monitoring" into active "management." Dr. Vinks recommend the lectures of Dr. Nicholas Holford from the University of Auckland, which are available on Dr. Holford's Web site, for more on the structural PK model formulas. The four types of models are structural, variability (between subject variability), error (residual variability), and covariate.

NONMEM looks at fixed effects—PK/PD parameters of the structural model (clearance, volume, etc.) and relationships between parameters and clinical factors—and random effects, which are interindvidual variability in clearance and volume, interoccasion variability in clearance and volume, and residual error on concentration. Past experience can be stored as a population model, such as elimination rate and volume of distribution.

Dr. Vinks called attention to the publication "Practical, Individualized Dosing: 21st Century Therapeutics and the Clinical Pharmacometrician" by Michael Neely, M.D., and Roger Jelliffe, M.D., which gives a good summary of the usefulness of pharmacometrics. Their Web site (lapk.org) has a number of useful articles on the subject.

The Reverend Thomas Bayes created the Bayesian Estimation, which is a statistical model that considers both prior and posterior probability. This model is central to pharmacometrics work.

Pharmacometrics and pop-PK/PD models are a key component for an array of applications in drug development and personalized care, are increasingly important in defining optimal dosing strategies in different populations, can be important extensions of therapeutic drug monitoring and help with clinical interpretation, and can be powerful tools in clinical trial design and simulation. Application of pharmacometrics will allow and improve exposure-effect targeting in patients. PK/PD patient-oriented informatics is still in its infancy, and new technologies and expert systems are necessary to facilitate access to interpretation and more widespread use (such as on the iPhone or iPad).

In response to a question from the fellows, Dr. Vinks said that the focus should be on both PK and PD, not just PK. PD is difficult, but it is very important, and marker information needs to be linked with outcome.

Pharmacometric Support for the Design and Analysis of Pediatric Trials (Phase I–III)

Edmund Capparelli, Pharm.D., University of California, San Diego

The difficulties of classical drug development in pediatric settings include the fact that there are limited resources available for study—there are few second chances for studies and pediatric studies are more expensive than adult studies. There is less certainty in optimal dosing—near adult systemic exposure may not be effective and may even have toxicity. The classical phase 3 studies are usually on a single dose, there is higher variability in pediatric subjects, and incentive requires approval from the European Medicines Agency and the FDA.

The FDA Pediatric Decision Tree is the guideline for the FDA for what types of studies need to be done. In pediatrics, other factors must be considered, including whether there is similar disease progression/dynamics, similar response to intervention, and whether it is reasonable to assume similar concentration response in pediatrics versus adults.

Pediatric diseases do not always progressively get worse. The pediatric pattern may be unique or substantially different from that of adults. There is a need to engage with subspecialists and think about disease dynamics and exposure-response in quantitative terms.

There are two approaches to predicting pediatric PK:

- A top-down approach predicts pediatric PK parameters from adults, can be used across various models, and applies size, function, and maturation to adults.
- A bottom-up approach, which predicts pediatric PK from *in vivo* information, uses typical PBPK models, and integrates extensive prior knowledge.

Pediatric model-based drug development (MBDD) is the standard because researchers often have existing information on drug and disease processes; because pediatric labeling is based on a limited number of studies, usually with no true phase 3 efficacy studies; and because studies can be focused to fill knowledge gaps. Modeling and simulation are then used to develop age-appropriate dosing; maximize information gained and trial success; and to improve communication between pharmacologists, statisticians, and clinicians. The use of modeling and simulation is part of the FDA Conceptual Framework for the Pediatric Initiative.

Pediatric pharmacometrics models include PK models, which provide metrics for exposure; PD models, which provide biomarker/surrogate endpoints; disease models; and study design models, which analyze dosing, population, adherence, placebo, and dropout information. The industry approach to pediatric PK studies involves the frequent use of pop-PK study designs and simulation for design and recommendations. There are several potential pitfalls:

- The use of an adult format for pediatric studies despite different objectives
- The lack of intensive studies to support structural of models
- Very limited data collected
- What information is collected is obtained through uninformative sample design
- The analysis is based on the adult template, which ignores the co-linearity of covariates, their impact on multiple PK parameters, and nonlinear developmental patterns.

Collaboration between pharmacologists and pediatric subspecialists can make certain that the questions are framed correctly with regard to the goal. This collaboration can also identify additional developmental questions that could be easily addressed and how the study could be incorporated into the clinical care setting.

Phase 1 studies in pediatrics differ from adult studies in many ways:

- It is important to integrate dosing and biomarker objectives.
- The dose will be "normalized" and nonfasting.
- PK sampling is sparse.
- Resistance to participation may be an issue.
- Urine is not as easy to collect.

The analysis is more likely to be compartmental, either with a population-based approach or a Bayesian one. Noncompartmental analysis makes few assumptions and can very quickly obtain results on an individual basis or on a small cohort, and the enrollment is often rate-limiting, so there is maximized data per subject. In population analysis, many subjects are needed to start, which is helpful when analyzing very sparse data, as in neonates. Population analysis allows the researcher to be opportunistic to locate a broader population and to integrate with other (adult) data.

Whereas phase 2 studies are conducted in adults to characterize exposure-response, gain safety information, and select dosage for phase 3, they are rarely done in pediatric drug development. Instead the objectives for phase 2 studies are usually rolled into components of phase 1 and phase 3 studies. However, it is important that phase 2 studies are conducted in pediatrics.

Phase 3 studies in adults seek to obtain information on efficacy and safety and to confirm earlier studies. Safety and efficacy are also objectives in phase 3 pediatric studies, but while some safety information can be extrapolated based on the adverse effects from adults, there are adverse effects unique to pediatrics, and issues of growth and development are further important to consider. Many times the information on effects is underpowered in pediatric studies. Pop-PK recognizes variability as important feature; seeks to explain variability by identifying demographic, physiologic, developmental, or drug-related factors; seeks to quantify the magnitude of the unexplained variability in the population; and can generate empiric Bayesian parameter estimates (post hoc) for individual subjects.

Drug-drug interaction (DDI) studies are rarely done in pediatrics because it is unethical to conduct them in healthy children, and crossover design in patients is problematic. The standard is to conduct phase 3 studies with pop-PK leveraged with existing adult data to understand drug interactions. Phase 3 design can be uninformative regarding exposure response for efficacy because it frequently involves a single-dose level, because of the impact of dose titrate to effect, and because the PK changes with age may be confounded with disease progression and response.

Key differences exist in study design and approaches for drug development in pediatrics compared with adults. Pharmacometrics provides a formal structure for leveraging of prior knowledge of drug metabolism, drug effects, and disease to improve pediatric clinical trial design and analysis. Informative pediatric studies result from close collaboration with pediatric subspecialists, adult pharmacologists, and other scientific disciplines.

Walk-Through Tutorial and Case Studies

Edmund Capparelli, Pharm.D., Jeffrey Barrett, Ph.D., Sander Vinks, Pharm.D., Ph.D.

Dr. Capparelli used case studies on efavirenz for HIV in infants and children less than 3 years and on lorazepam to illustrate the use of PK in determining in dosing.

Dr. Barrett presented a detailed software demonstration of NONMEM and Pharsight Clinical Trial Simulator. NONMEM can be used in conjunction with Pharsight. He stressed that there is a large user community and support available to assist users. This software provides the opportunity to make perturbations to understand the range of possibilities—the purpose of simulations. The aim is to write good protocols, justify them based on modeling, and be rigorous in terms of the analysis and design of the experiments.

Dr. Vinks discussed MW/Pharm 3.6 (Windows-based 4.0), which comprises a database with PK parameters of 180 drugs, a medication history database, and procedures for an individual drug dosage regimen calculation. The included curve-fitting facilities allow estimation of PK parameters on the basis of medication history, taking into account a varying status of the patient with respect to body weight and kidney function, optionally using a Bayesian procedure. The module KinBes performs the evaluation of bioavailability studies, including various methods, and an extensive statistical evaluation of bioequivalence. The fellows gave inputs for the program to create a patient and scenario, which Dr. Vinks used to demonstrate how the software works. There are a variety of tools available for use. In response to a question from the fellows as to how to determine which tool is best to use, Dr. Vinks referred to the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (www.iatdmct.org), which as a pharmacometrics group that could give guidance regarding the advantages and disadvantages of different tools. However, the best way to determine usefulness is to use the different programs and, through trial and error, see which best suits the needs at hand.

Overview of the *PedPharmHub*

Deborah Stein, M.A., Circle Solutions, Inc.

Ms. Stein gave a demonstration of the *PedPharmHub*, which uses Microsoft SharePoint, a Web application platform that provides a central location for storing and collaborating on documents, which can significantly reduce the use of e-mail and conference calls for communication. Documents can be stored and edited, with version control to keep track of the different versions created and edited by different users. There is also a discussion board feature to aid in the exchange of ideas. Everyone will be e-mailed user names and passwords for personal, secure access to the site. Dr. Giacoia stressed that this site is for the fellows and will only be as good as they make it. There were several suggestions from the fellows to improve the site:

- Create separate, secure rooms for confidential information exchange.
- Create separate folders with restricted access.
- Record journal clubs for posting on the site to be listened to as podcasts later.
- Record lectures for posting on the site to be listened to as podcasts later.
- Create a “virtual” journal club.
- Create an Ask the Expert area, where people can pose questions for answers by experts in that area.

Conclusion

Dr. Giacoia again stressed the importance of the Principles of Clinical Pharmacology lecture series and asked that all the fellows make it a priority to ensure its success.

Participant List

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Benjamin Black, M.D.
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Jacob Brown, Pharm.D.
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Edmund Capparelli, Pharm.D.
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M. Elena Rodriguez, M.D., Ph.D.
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David Siegel, M.D.
Perdita Taylor-Zapata, M.D.
Ekaterini Tsilou, M.D.
Kevin Turner, M.D.
Neha Vaghasia, M.D.
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