Pharmaceutical Department

2018

Annual Report

2018 Annual Report
Pharmaceutical Department

Faculty: Full Members: William E. Evans, PharmD; William Greene, PharmD; Mary V. Relling, PharmD (chair); Erin G. Schuetz, PhD; John D. Schuetz, PhD (vice-chair); Clinton F. Stewart, PharmD; Associate Members: James M. Hoffman, PharmD; Jun J. Yang, PhD; Assistant Members: Daniel Savic, PhD; Liqin Zhu, PhD

Laboratory Directors: Alejandro Molinelli, PhD; Kristine R. Crews, PharmD

Fellows: Jordan Beard, PhD; Rebba Boswell-Casteel, PhD; Christopher Coke, PhD; Rebecca Crawford, PhD; Jonathan Diedrich, PhD; Li Fan, PhD; Daniel Ferguson, PhD; Emily Finch, PhD; Yoshihiro Gocho, MD, PhD; Tomoka Gose, PhD; Laura Hamel, PhD; Charnise Goodings-Harris, PhD; Yizhen Li, PhD; Yiwei Liu, PhD; Takaya Moriyama, MD, PhD; Maoxiang Qian, PhD; Juwina Wijaya, PhD; Hui Zhang, MD, PhD

Residents: Amanda Gillispie, PharmD; Keito, Hoshitsuki, PharmD; Kristen Hughes, PharmD; Hannah Sauer, PharmD

Graduate Students: Kavya Annu, R.J.Autry, Anthony Brown, Alessio Cozzarolo, Ashley Crumby, Samit Ganguly, Jianzhong Hu, Chuang Jiang, Nick Keeling, Xujie Zhao, Chan Zou

Computational Staff: Nancy Kornegay**,** Andrey Matlin, Claire Mills, Carl Panetta, Colton Smith, Wenjian Yang,

Staff Scientists: Erik Bonten, PhD**;** Barthelemy Diouf, PhD; Amarjit Chaudhry, PhD; John Lynch, PhD; Yu Fukuda, PhD

Pharmacist leadership: David Aguero, PharmD; Delia Carias, PharmD; Kelly Caudle, PharmD, PhD; Wendell Cheatham, DPh; Cyrine Haidar, PharmD; William Humphrey, DPh, MS, MBA; John McCormick, PharmD; Steve Pate, DPh; Jennifer Pauley, PharmD; Jennifer Robertson, PharmD; Barry Williams, BS Pharm

Clinical Pharmacy Specialists: Liz Hall, PharmD; PJ Barker, PharmD; Allison Bragg, PharmD; Andy Christensen, PharmD; Richard Clark, PharmD; Shane Cross, PharmD; Clay Daniels, PharmD; Melissa Quinn, PharmD; Hope Swanson, PharmD; Deborah Ward, PharmD

Pharmacists: Chris Askins, PharmD; Susan Carr, PharmD; Robbin Christensen, BS Pharm; Monty Coleman, BS Pharm; Hana Danzi, MS Pharm; Nousheen DeRenzo, PharmD; Debra Ethridge, PharmD; Joseph Evans, PharmD; Liz Gallimore, PharmD; Amy Harris, PharmD; Jennifer Kemper, PharmD; Jenny Knych, PharmD; Chuck Longserre, PharmD; Shane Marshall, PharmD; Jennifer Mason, PharmD; Anne McCormick, BS Pharm; Tommy Mills, PharmD; Tiffany Nason, PharmD; Tanya Nguyen, PharmD; Monica Patel, PharmD; Trina Peery, PharmD; Jackie Quackenbush, BS Pharm; Julie Richardson, PharmD; Linda Schiff, PharmD; Chris Scobey, PharmD; Camille Smith, PharmD; Kevin Smith, PharmD; Tabetha Todd, PharmD; Deni Trone, PharmD; Dagny Ulrich, PharmD; Gayle Westmoreland, BS Pharm; Cheri Wilkerson, PharmD; Elizabeth Wilson, PharmD; Matthew Wilson, PharmD; Curtis Yeh, PharmD; Keith Young, PharmD

Overview:

The overall mission of the Pharmaceutical Department is to discover the basis for inter-individual differences in response to medications, to translate research findings to improve treatment outcomes, and to provide the best and most comprehensive pharmaceutical care for our patients. The Pharmaceutical Department comprises Pharmaceutical Sciences (with a primary mission of research), and Pharmaceutical Services (with a primary mission of clinical care). Both research and treatment are highly intertwined at St. Jude, and this integration exists within other academic departments at SJCRH that have a dual mission of patient care and research. Many of our departmental faculty and staff members are extensively involved in both research and patient care. Indeed, the synergies and efficiencies of having the research and service components in a single academic department have been hallmarks of SJCRH since it was established in 1962, and facilitates the success of our institution.

Our vision is to be a premier academic department in pharmaceutical sciences, encompassing clinical pharmaceutical care and research, with special expertise on therapeutics relevant for children with catastrophic diseases. Survival rates for children with cancer, hematologic disorders, HIV infection, or other serious diseases continue to increase, largely through the improved use of medications. Failure of current therapies and unacceptable adverse effects are partly due to less-than optimal prescribing. Our goal is to elucidate the biological basis of interindividual differences in pharmacologic response, and to translate our findings into improving patient care.

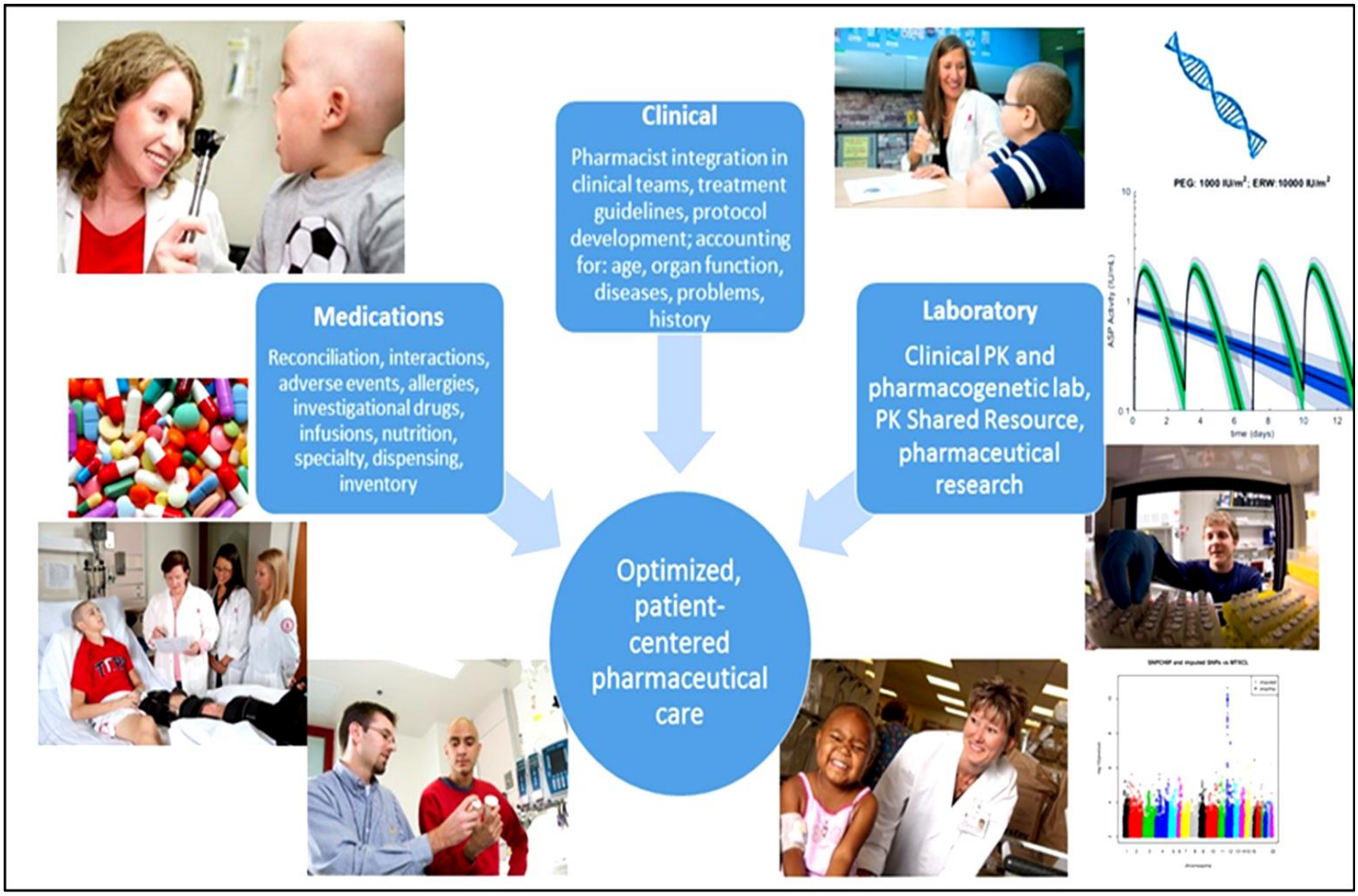

Figure 1. *With responsibility for medications, the use of clinical data, and the development of clinical and research laboratory tests, knowledge is used to provide the best possible care for St. Jude patients while making discoveries with implication outside of St. Jude.*

Heterogeneity in the metabolism, transport, elimination, targets, and receptors of many drugs and consequent variability in therapeutic or adverse effects may result from germline genetic differences or genetic alterations in malignant cells. Drug response is also influenced by nongenetic factors (e.g., drug interactions, host organ function and maturity, disease severity, adherence to therapy).

We develop preclinical models to systematically characterize the determinants of human variation in drug response, and we integrate our work into translational clinical studies (Figure 1). Laboratory work informs clinical studies, and clinical problems drive much of the laboratory work.

Faculty members lead and participate in interdisciplinary St. Jude programs and national cooperative research collaborations. Our pharmacogenetic research integrates genome-wide analyses, molecular analyses, functional genomics, pharmacokinetics, and pharmacodynamics to identify genetic determinants of drug effects, with the long- term goal of optimizing therapy for individual patients. The Department has ten faculty members, 15-25 post-doctoral fellows (Figure 2) and residents (Figure 9), 10-20 undergraduate and graduate students, over 45 pharmacists, and over 110 full time staff members working as computing experts, research nurses, technical, laboratory, administrative, and clinical staff. The department is supported by multiple NIH grants. The research in the department includes clinical and fundamental pharmacology, pharmacokinetics, pharmacodynamics, and pharmacogenomics, and is described under the following sections for each faculty member. Pharmaceutical Sciences occupies over 15,000 sq. ft. of contiguous state-of-the-art equipped laboratory and office space, and Pharmaceutical Services occupies over 18,000 square feet of space in the clinical areas of St. Jude. The department hosts weekly research workshops and journal clubs that are open to the entire institution and are widely attended by colleagues outside the department, in addition to multiple laboratory or Services specific meetings, webinars with national and international colleagues, and regular pharmacogenomics meetings.

Figure 2*. Post-doctoral fellows 2017-2018* ***Back row****: Joshua Hess, Yizhen Li, Stefanie Baril, Yoshihiro Gocho, Daniel Ferguson, Jordan Beard, and Charnise Goodings Harris.* ***Front Row****: Jingliao Zhang, Takaya Moriyama, Li Fan, Yiwei Liu, Emily Finch, Wentao Yang, Rina Nishii, Sabina Ranjit, and Tomoka Gose.*

Details on the rich St. Jude environment for clinical care and for clinical and basic research are available at www.stjude.org.

Pharmaceutical Department faculty, staff, and trainees work closely with each other; with our collaborators in other departments at St. Jude; and with colleagues around the world on basic translational, and clinical research projects and to provide outstanding pharmaceutical care to St. Jude patients.

Faculty:

William E. Evans, PharmD

Research in the Evans lab is focused on the pharmacogenomics of anticancer agents, with an emphasis on childhood acute lymphoblastic leukemia (ALL) (reviewed in Evans and Relling, *Nature* 2004; Pui and Evans, *NEJM* 2006; Paugh et al, *Clin Pharmacol Ther* 2011; Relling and Evans, *Nature* 2015). Several approaches are currently being used to identify genes and genome variations that are important determinants of the disposition and effects of antileukemic agents, including the use of genome wide approaches such as gene expression profiling (mRNA, microRNA) and RNA-sequencing of leukemia cells coupled with, genome-wide SNP (germline and somatic) and CnG-methylation analyses and whole exome/genome sequencing of patient cohorts that have been uniformly treated and evaluated on prospective clinical trials at St. Jude Children's Research Hospital (reviewed in Evans and Relling, *Nature* 2004), or by our collaborators in the COG and in Europe (e.g. Princess Maxima Center, Utrecht). Ongoing studies are investigating genes that the lab has linked with resistance to antileukemic agents (Figure 3) (Holleman et al, *NEJM* 2004; Lugthart et al, *Cancer Cell* 2005), and genes linked to the disposition (Kager et al, *JCI* 2005; Zaza, *Blood* 2005) or pharmacologic targets (Diouf et al, *JAMA* 2015; Paugh et al, *Nat Genet* 2015) of antileukemic agents as well as the influence of somatic and karyotypic abnormalities on genotype-phenotype concordance (Cheng, *Nature*

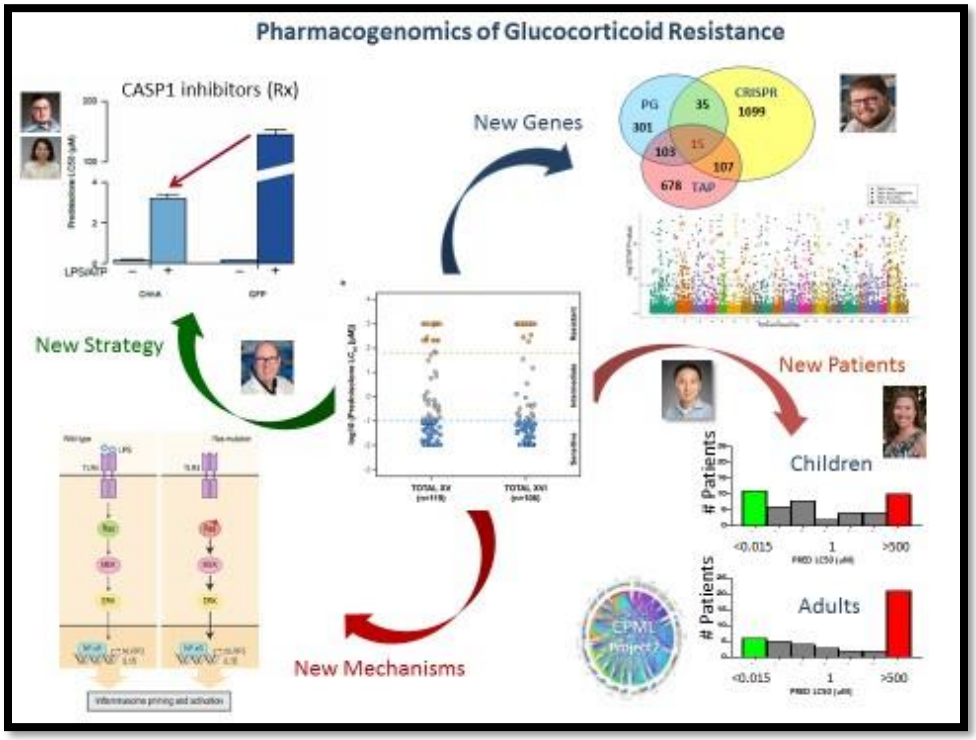

Figure 3: CASP1 causes glucocorticoid resistance via glucocorticoid receptor cleavage. We are building on our prior discovery that increased expression of inflammasome components CASP1 and NLRP3 via somatic hypo-methylated promoter regions in leukemia cells leads to glucocorticoid receptor cleavage by CASP1 and glucocorticoid (GC) resistance (see Paugh et al, Nature Genet 2015). We have now found evidence that this mechanism of GC resistance is operative in leukocytes of patients with chronic kidney disease who are refractory to GC treatment. We have more recently found a higher frequency of GC resistance in adult ALL, and are investigating whether the CASP1 mechanism is responsible. We are also pursuing high-throughput screens to identify small molecule inhibitors of CASP1 as a strategy to mitigate this mechanism of GC resistance, and enhance treatment response.

Genetics 2005; Diouf et al, *Nature Med* 2011). We have recently worked in collaboration with our biostatistics colleagues to develop a pipeline for integrating multiple (six) genomic and epigenetic features (noted above) on a gene centric basis to identify genes and genomic variants that determine the resistance of primary ALL cells to glucocorticoids. We are now extending this strategy to 14 classic and more-targeted antileukemic agents to elucidate the genomic basis of de novo and acquired resistance to antileukemic agents (in collaboration with the Jun Yang lab). The lab is also working to extend our prior discovery of inherited variants in *CEP72* that predispose to vincristine-induced peripheral neuropathy, pursuing mechanistic studies in iPSC-neurons, interrogating rare variants and assessing the influence of CEP72 and other inherited variants on persistent neuropathy in adult survivors of childhood ALL (in collaboration with Dr. Kiri Ness). We are also investigating therapeutic strategies to mitigate acute neuropathy in mouse models of vincristine neuropathy (in collaboration with colleagues in Developmental Neurobiology). Work in the lab is funded by a long-standing R01 from NCI (CA36401, W. Evans, PI), a project in the Center for Precision Medicine P50 Grant from NIGMS as part of the NIH-funded Pharmacogenetics Research Network (GM115279, M. Relling PI), by a Cancer Center Support grant from NCI (CA21765 C. Roberts, PI), and by ALSAC, the fundraising organization for St. Jude Children's Research Hospital. The lab comprises a number of post-doctoral fellows, graduate students, , research technologists, bioinformaticists, computational scientists and staff scientists , working with collaborators at St. Jude (including Mary Relling, Ching-Hon Pui, Charles Mullighan, K. Roberts, Hiroto Inaba, Kirsten Ness and Jun J. Yang as major collaborators, plus additional physicians, clinical pharmacists, research nurses and other staff at St. Jude), and with collaborators at other institutions in the US (HudsonAlpha, University of Chicago) and Europe (Erasmus University, Princess Maxima Center). The lab's overall goals are to elucidate genomic determinants of toxicity and efficacy of anticancer agents and translate this knowledge into new diagnostics and treatment strategies to optimize the therapy of ALL (Relling and Evans, *Nature* 2015; Dunnenberger et al, *Ann Rev Pharmacol Tox* 2015).

William Greene, PharmD

I joined Pharmaceutical Services as Chief Pharmaceutical Officer in August 2007. I have had a long career as a clinical pharmacy practitioner and leader in development of drug policy in hospital- based practice. My interests have been diverse and are summed up in the goal of developing structures, personnel, policy and practice to accomplish the best possible system to assure optimal outcomes of pharmacotherapy. My interests in infectious diseases, pharmacokinetics, performance improvement and medication safety continue.

As the senior leader of Pharmaceutical Services, it is my goal to assure the best possible design and function of pharmacy services to assure that we achieve the desired outcomes of drug therapy for St. Jude patients. To this end, Pharmaceutical Services collaborates closely with other disciplines in providing patient care, and with clinicians and scientists in translational and clinical research, and employs the principles of continuous process improvement in ongoing refinement/improvement of patient-related services. Clinical research in Pharmaceutical Services focuses on applying pharmacokinetic, pharmacogenetic, and therapeutic drug monitoring principles to patient care, and in improving the safety of medication use. I currently retain a faculty appointment with the University of Tennessee College of Pharmacy (Professor, Affiliated), and am active in national and state professional organizations (American College of Clinical Pharmacy, American Society of Health Care Systems Pharmacists, and Tennessee Pharmacists Association).

James M. Hoffman, Pharm

I joined the Pharmaceutical Department in 2004, and the St. Jude Faculty in 2011. My career has focused on evaluating and improving complex medication use systems, and I currently provide leadership to evaluate and improve a range of patient care processes through my role as the hospital's Chief Patient Safety Officer within the Office of Quality and Patient Care. My research is focused on patient safety event detection, patient safety culture, and clinical decision support.

Our work on patient safety event detection and reporting systems is built on our department's leadership to develop and implement St. Jude's novel electronic event reporting system software (EERS). EERS is used to report all patient safety events at St. Jude, and this system has resulted in a 20% increase in event reporting. Because a healthy patient safety culture is essential to safe care, we have focused on assessing patient safety culture at St. Jude and devised new tools to measure specific aspects of safety culture in the hospital setting (Petschonek S et al *J Patient Saf 2014* and Burlison JD et al *J Patient Saf 2014*).

I also lead a variety of efforts to expand and improve the use of clinical decision support (CDS) in the electronic health record (EHR). Through the PG4KDS protocol, St. Jude is a leader in incorporating pharmacogenetic data and associated CDS into the EHR (Bell et al, JAMIA, 2013; Hicks et al AJHP, 2016) (Figure 4), and I have contributed to this protocol as an investigator since its inception. I have also been actively engaged in the Clinical Pharmacogenetic Implementation Consortium (CPIC) since its inception, and I co-lead the CPIC Informatics Working Group since its inception in 2013. CPIC has devised vendor agnostic implementation resources which are available for each guideline (Hoffman et al. *JAMIA*, 2016). CPIC also recently lead a consenus process to standardize pharmacogenetic terms. These terms arebeing widely adopted by both clincal laboratory and informatics communities and will help facilitate sharing pharmacogenetic results across disparate clinical information systems. (Caudle et al. *Genet Med*. 2016) More recently, we have studied payer perspectives on pre-emptive pharmagenetics to understand how to remove reimbursement as a barrier to pharmacogenetic testing (Keeling et al. *Genet Med.* 2017) and summarize how standardization can accelerate the adoption of pharmacogenomics (Caudle et al. *Pharmacogenomics* 2018).

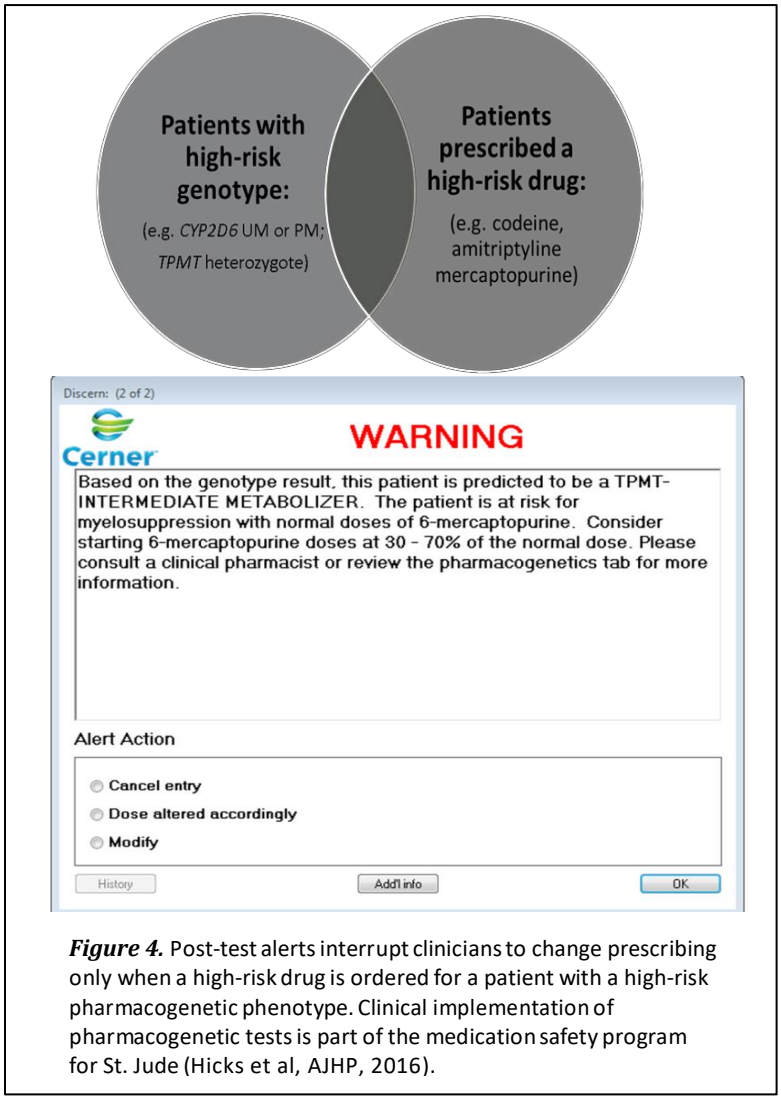

Figure 4. Post-test alerts interrupt clinicians to change prescribing only when a high-risk drug is ordered for a patient with a high-risk pharmacogenetic phenotype. Clinical implementation of pharmacogenetic tests is part of the medication safety program for St. Jude (Hicks et al, AJHP, 2016).

Mary V. Relling, PharmD

I have been a faculty member in the Pharmaceutical Department at St. Jude since 1988 and chair of the department since 2003. The majority of my discovery research efforts have been directed to translational research in childhood acute lymphoblastic leukemia (ALL), to identify the host- and treatment-related risk factors for adverse treatment outcomes in ALL. I also maintain clinical involvement at St. Jude and in the Children's Oncology Group (COG). The clinical problems faced by children with ALL drive my research. Much of the work of my laboratory focuses on finding the genetic basis of why patients differ from one another in their risk of adverse effects of therapy, both drug toxicities and ALL relapse. I co-lead the Center for Precision Medicine in Leukemia (CPML), a multidisciplinary research group (http://www.pgrn.org/precision-medicine-in-leukemia.html). We also study how non-genetic factors (e.g., diet and drug interactions, kidney and liver function, and age) affect how patients differ from each other in response to medications.

The ALL phenotypes we focus on most include relapse, glucocorticoid induced osteonecrosis (Figure 5), asparaginase immunogenicity and pharmacodynamics, and hepatotoxicity (e.g. Liu C et al, *JCO,* 2016; Liu Y et al, *Clin Pharm Ther* 2017). Our laboratory has a heavy reliance on computational approaches, as we use genome-wide tools to interrogate genetic variability.
We also use chemical analyses (e.g. HPLC, LC/MS) to study medication pharmacokinetics, cell culture models, molecular biologic techniques, murine models, and analysis of clinical outcomes and phenotypes.

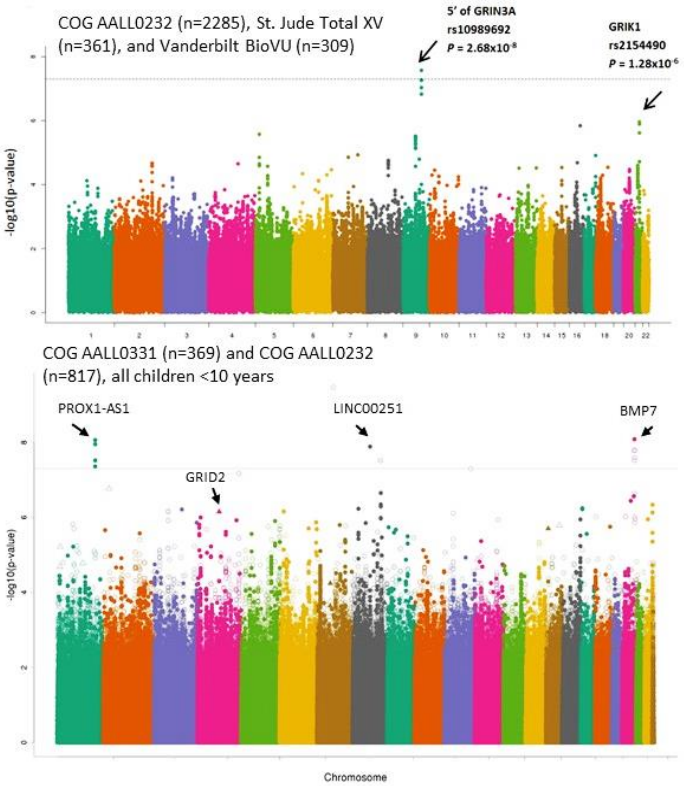

Figure 5. Manhattan plots of inverse log p values for associations of germline SNPvariants with risk of osteonecrosis in patients with ALL and in adults without ALL (top panel, Karol et al 2015) and in patients younger than 10 years of age (bottom panel, Karol et al, 2016). Variants in glutamate receptor genes were associated with osteonecrosis in all cohorts.

In addition to discovery research, we lead work to implement preemptive clinical pharmacogenomic testing. This is accomplished locally at St. Jude via a clinical protocol, PG4KDS (www.stjude.org/pg4kds) and internationally via the Clinical Pharmacogenetics Implementation Consortium (CPIC®, www.cpicpgx.org) (Caudle et al *Genet Med* 2017), an NIH-supported genomics resource. Our staff help lead efforts to create and curate gene/drug pair CPIC prescribing guidelines. St. Jude played a leading role in the recent update of the CPIC guideline for thiopurines, which now

includes *NUDT15* in addition to *TPMT* (Relling et al *Clin Pharmacol Ther* 2018). We collaborate with many investigators within the department, throughout St. Jude, within the COG, and within the Pharmacogenomics Research Network (PGRN).

Erin G. Schuetz, PhD

I joined the St. Jude Pharmaceutical Department in 1993. My lab studies cytochromes P450 (CYP) and other enzymes that metabolize many of the drugs administered to St. Jude patients. The lab identifies genetic determinants explaining variation in hepatic and intestinal CYP and AOX activities and, hence, variation in drug efficacy, toxicity and, ultimately, therapeutic outcome. The lab strategically uses both the candidate gene approach and exploits network and pathway analysis tools to illuminate the genetic variation in novel candidate genes affecting the CYP genetic network. The liver system biology/network approach has identified the node genes that, when individually perturbed, co-regulate many genes in the CYP network. My lab then uses deep resequencing of these novel candidate genes, and allelic expression imbalance analysis, to identify the functional and regulatory variants responsible for altering CYP activity and driving changes in the CYP expression network. Standard molecular, cellular and biochemical studies are then used to determine the functional consequence of these variants. Retrospective association studies are performed to determine if functional variants in candidate genes translate to clinical differences in CYP mediated drug clearance.

Most recently our studies have focused on studying the impact of Vitamin D3 (VD3) sufficiency versus insufficiency on survival and chemotherapeutic efficacy and toxicity in a mouse model of acute lymphoblastic leukemia with the BCR-ABL fusion gene. These studies were prompted by the fact that a significant percentage of the pediatric population is VD3 deficient or insufficient, and that VD3 levels are further eroded during therapy because anti-chemotherapeutic regimens decrease the levels of the biologically active form of vitamin D3. Hence a major long-term consequence is a loss of bone mineral density in these pediatric patients during their peak bone building years. As a result, clinical trials have been initiated to determine whether vitamin D supplementation can correct VD3 insufficiency and improve bone density in children treated for leukemia. However, there was also a concern that vitamin D supplementation might cause drug interactions with medications metabolized by some drug metabolizing enzymes and drug transporters because the expression of some of them is regulated by VD3. Our results found that VD3 supplementation had no effect on the pharmacokinetics of glucocorticoids. However, because our results demonstrated a significant effect of VD3 on survival of mice from the BCR-ABL+ leukemia, and that the combination of VD3 and glucocorticoid therapy may prove beneficial in treating BCR-ABL+ leukemia, efforts are underway to determine the mechanisms by which VD3 mediates these effects.

John D. Schuetz, PhD

A member of the Pharmaceutical Department since December 1992, my laboratory focuses on understanding the contribution of ABC transporters to pathological processes and pharmacological response using cell culture model systems as well as gene knockout models (e.g., reviewed *Ann Rev Pharm Tox,* 2006 and 2013). Using these model systems, we have, through collaborative effort with other SJCRH investigators, identified one ABC transporter as an important stem cell marker (Zhou et al, *Nat Med,* 2001, Zhou et al, *PNAS*, 2002) that has a prominent role in hematopoietic cell survival under hypoxia (Krishnamurthy et al, *J Biol Chem*, 2004) as well as myeloid leukemia (Fukuda et al, *JCI Insight*, 2017). We extended these studies to establish a knockout mouse which revealed for the first time that the ABC transporter (ABCC4/Mrp4) was important in protecting the brain from

penetration of chemotherapeutic agents (Leggas et al, *Mol Cell Biol*, 2004). One could infer from these findings that the therapeutic efficacy of CNS-directed drugs that are Mrp4 substrates may be improved by developing Mrp4 inhibitors. The ABCC4/Mrp4 transporter was first functionally defined by my laboratory (Schuetz et al, *Nat Med*, 1999) and was demonstrated to protect hematopoietic cells from injury due to the widely used immunosuppressive and cancer chemotherapeutic agent 6-mercaptopurine. This finding allowed us through collaborative efforts within the department (Evans, Relling, E. Schuetz) to identify a defective ABCC4 allele that was prevalent in the Asian population, thus providing an explanation for the anecdotal reports of enhanced sensitivity to the toxic hematopoietic side-effects of 6 mercaptopurine in this population (*Krishnamurthy* et al, *Cancer Res,* 2008). Further studies suggest ABCC4 has a strong role in CFTR (Li, et al, *Cell*, 2007) and also in modulating platelet aggregation as well as response to anti-platelet drugs (Cheepala, Pitre, et al, *Blood* 2015). Other studies have focused on a mitochondrial and plasma membrane ABC transporter we first characterized (Krishnamurthy et al, *Nature*, 2006; Fukuda et al, *J Biol Chem*, 2011) that protects cells from oxidative stress (Lynch et al, *Cancer Res,* 2009) and also is a key genetic modifier of porphyrin, a disease of disrupted heme synthesis (Fukuda et al, *Nat Comm*, 2016). Because over a third of ABC transporters contribute to disease processes, our goal has been to understand the role of these genes in pathological conditions, such as our recently described roles for the bile acid transporter, *Abcb11,* in protecting against neonatal respiratory distress (Zhang et al*, Nat Comm, 2015*). From this perspective, we have also been elucidating how select ABC transporters contribute to cancer (medulloblastoma) (Morfouace et al, *Cancer Res*. 2105) and therapeutic response (Pitre et al, *Nat Comm*, 2017).

Clinton F. Stewart, PharmD

I joined the Pharmaceutical Department at St. Jude in 1991, and since then have focused my research efforts in developmental therapeutics for children with solid malignancies and central nervous system (CNS) tumors. In the clinic, my research involves the application of state of the art pharmacokinetic (individual and population), pharmacogenetic, and pharmacodynamic approaches to understanding the variability in drug disposition in children with cancer. Little is known about the disposition of anti-cancer agents in infants and young children less than 3 years of age, which often leads to increased risk of morbidity, poor tumor control, and increased incidence of late effects. Thus, we have embarked on a comprehensive series of pharmacokinetic, pharmacogenetic, and pharmacodynamic studies to understand how

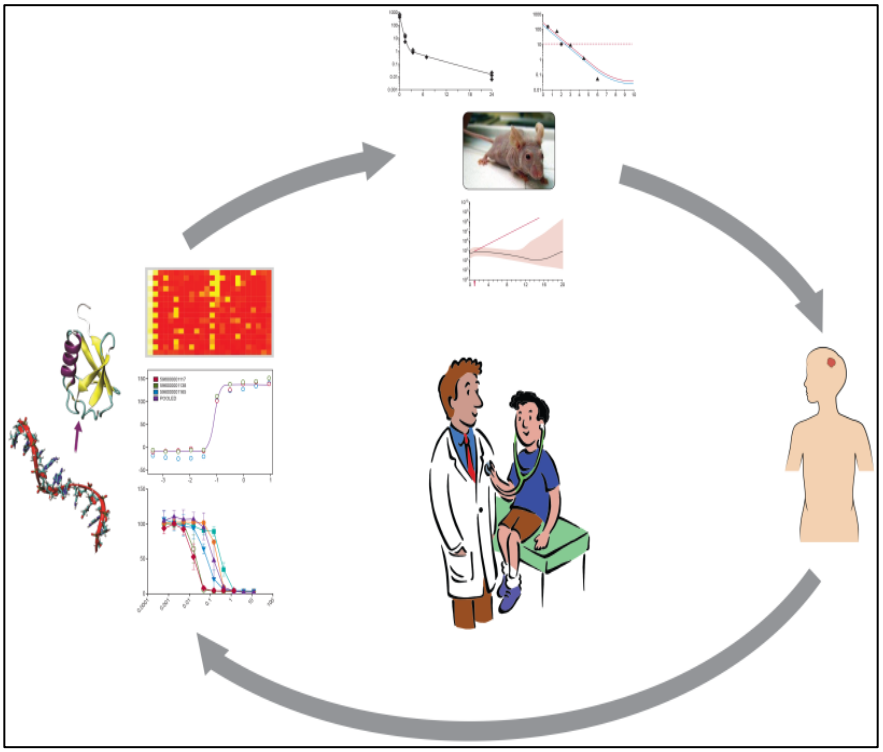

Figure 6. Schematic overview of our approach to using pharmacokinetic modeling and simulation in the identification of new anticancer drugs for treatment of pediatric CNS tumors.

developmental changes in infants and young children affect the disposition and toxicities of anticancer drugs used in the treatment of infants with malignant brain tumors. Our long-term goal is to determine rational dosing regimens for infants and young children by better understanding the developmental pharmacology of anti-cancer drugs and to apply these regimens to therapy for other childhood malignancies and chronic medical conditions. In addition to these clinical studies we perform at St. Jude, my lab collaborates with investigators within the Pediatric Brain Tumor Consortium and the Children's Oncology Group.

Our work in the laboratory is guided by addressing clinically relevant problems encountered in the therapy of children with brain tumors (e.g., CNS drug penetration in brain tumors). The studies in the lab are designed to either yield data that can be translated into the design of improved clinical trials or to answer questions generated in the clinic. For example, the treatment of children with primary CNS tumors continues to be a challenge despite recent advances in technology and diagnostics. A variety of issues unique to pediatric CNS tumors impede development and clinical success of novel therapies, and for this reason, safe and effective treatments remain elusive. The preclinical approach we use (Figure 6) employs tumor subgroup-specific models of pediatric CNS tumors, cerebral microdialysis sampling of tumor extracellular fluid (tECF), and pharmacokinetic modeling and simulation to overcome challenges that currently hinder researchers in this field.

Jun J. Yang, PhD

I joined the St. Jude faculty in 2010 and I am currently an Associate Member in the Pharmaceutical Department. The research focus of my group is pharmacogenomics of treatment outcomes (e.g. relapse) and toxicity in children with childhood acute lymphoblastic leukemia (ALL). Primarily taking a genome-wide approach, we identify genetic variations that contribute to interpatient variability in response to ALL therapy. By doing so, the goals of our research are to elucidate biological pathways dictating response to antileukemic drugs, to identify genetic predictors for drug resistance which can be utilized for treatment individualization, and to develop novel therapeutic agents to overcome drug resistance. Because genetic factors in both host and tumor genome can affect drug response, my lab has focused on characterization of inherited (germline) and acquired (somatic) genetic factors that are associated with treatment response in childhood ALL. We have led the first genome-wide association study to identify germline genetic variations associated with minimal residual disease in response to remission induction therapy in children with ALL (Yang et al, *JAMA,* 2009) and the first genome-wide interrogation of copy number alterations related to ALL relapse (Yang et al, *Blood,* 2008). We are particularly interested in the genetic basis for racial/ethnic differences in ALL treatment outcomes and disease susceptibility, e.g. we performed genome-wide studies to characterize ancestry-related genetic variants (Perez-Andreu et al, *Nat Genet* 2013*, J Clin Oncol* 2012, *J Natl Cancer Inst* 2013) that contribute to higher risk of relapse in Hispanic children with ALL (Yang et al, *Nat Genet*, 2011). We are also interested in pharmacogenetics of treatment toxicity, especially thiopurine-related myelosuppression (J Clin Oncol 2015, Nat Genet 2016). Our group is part of the NIH Pharmacogenomics Research Network (PGRN) and the Center for Precision Medicine for Leukemia (CPML).

Daniel Savic, PhD

I joined the Pharmaceutical Department at St. Jude Children's Research Hospital in August of 2016. Prior to my faculty appointment at St. Jude, I was a member of the Encyclopedia of DNA Elements (ENCODE) consortium, a large, multi-center, collaborative effort that aims to functionally annotate the human genome. To better understand genome structure and function, I applied a variety of functional genomic techniques and next-generation reporter assays (Savic et al. *Genome Research* 2015, Savic et al. *Genome Medicine* 2016, review in Engel et al. *Semin Cell Dev Biol* 2016, Ramaker and Savic et al. *Genome Research* 2017), and further engineered novel ChIP-seq based technologies that expand the utility (Savic et al. *Epigenetics and Chromatin* 2013) and enhance the capacity (Savic et al. *Genome Research* 2015) of the ChIP-seq functional genomic assay.

My laboratory at St. Jude focuses on the pharmacogenomics of treatment in pediatric acute lymphoblastic leukemia (ALL) in order to better understand the molecular underpinnings of anticancer drug resistance and disease relapse. Our group aims to address a fundamental and critical question in ALL pharmacogenomics: how does the noncoding regulatory genome impact antileukemic drug resistance and disease relapse? Our laboratory works on three interrelated projects that involve: (1) elucidating the role of noncoding, gene regulatory elements in antileukemic drug resistance, (2) functionally characterizing noncoding sequence variants at genomic loci associated with ALL treatment outcome, and (3) developing novel, high-throughput assays to phenotypically screen noncoding sequences. We are also part of the Pharmacogenomics Research Network (PGRN), as well as the Center for Precision Medicine in Leukemia (CPML).

Liqin Zhu, PhD

I joined the Pharmaceutical Department as a Research Associate in 2016 and was promoted to an Assistant Member in 2017. I previously studied tissue stem cells in global cancer initiation (Zhu *et al*. *Nature* 2009; *Cell* 2015; *Cell* 2016). My current research program focuses on elucidating the cellular and molecular mechanisms driving the metastasis of pediatric hepatoblastoma (HB) and hepatocellular carcinoma (HCC). We use three main approaches: (1) establish patient-derived organoid (PDO) models for HB and HCC and discover novel diagnostic and prognostic biomarkers via comprehensive genomic profiling; (2) study the functions of candidate genes in HB and HCC metastasis using PDO and orthotopic transplantation mouse models; and (3) identify new treatment for metastatic HB and HCC via PDO-based drug screen. Our preliminary study has demonstrated the ability of HB and HCC organoids to generate highly invasive and metastatic tumors in vivo which faithfully recapitulated recurrent and metastatic tumors in patients (Li *et al*, *Am J Pathol* 2018). Our transcriptomic study has identified a small number of genes that are significantly associated with HB and HCC metastasis. We are currently testing the biological functions and therapeutic values of these candidate genes in PDO and orthotopic mouse models. Our long-term goal is to develop novel therapeutics for the aggressive forms of pediatric liver cancer via detailed biological dissection of the disease progression and metastasis.

Pharmaceutical Services

Pharmaceutical Services is led by Dr. William Greene and is staffed by pharmacists, pharmacy technicians, research and administrative staff, and faculty, (see Organization Chart at end) all dedicated to helping patients. St. Jude Pharmaceutical Services focuses on providing the best pharmaceutical care required for each child at SJCRH while supporting a collective research endeavor. Our personnel, working with other caregivers in a cutting-edge collaborative environment assure the best possible outcomes of drug therapy. Nearly 140 pharmacists, technicians, and other support personnel are involved in the care of patients and support of clinical research at St. Jude, helping to fulfill our organizational mission to "advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment."

Pharmaceutical Services addresses St. Jude patients across the continuum of care – providing services while they are inpatients, in the outpatient clinic, and while in domiciliary facilities or at home. Inpatient services include Clinical Pharmacist collaboration in management of patients of all major clinical patient care groups, including Leukemia/Lymphoma, Solid Tumor, Neuro-Oncology, Bone Marrow Transplant, Hematology, and HIV services. After discharge from the hospital, these patients are seen in outpatient clinics located on campus where pharmacists are directly involved with provider teams. In these settings, clinical pharmacists collaborate in the care of these patients, including the ordering of medications and laboratory tests, the development of clinical treatment protocols, provision of drug therapy and nutritional support consults, and assessment and management of the long-term effects of medication therapy. An on-site infusion center pharmacy provides medications for outpatients, and is fully staffed by pharmacists. On average, there are approximately 350 patient clinic visits per day, with 110 infusion center encounters, leading to the dispensing of over 700 prescriptions or doses per day.

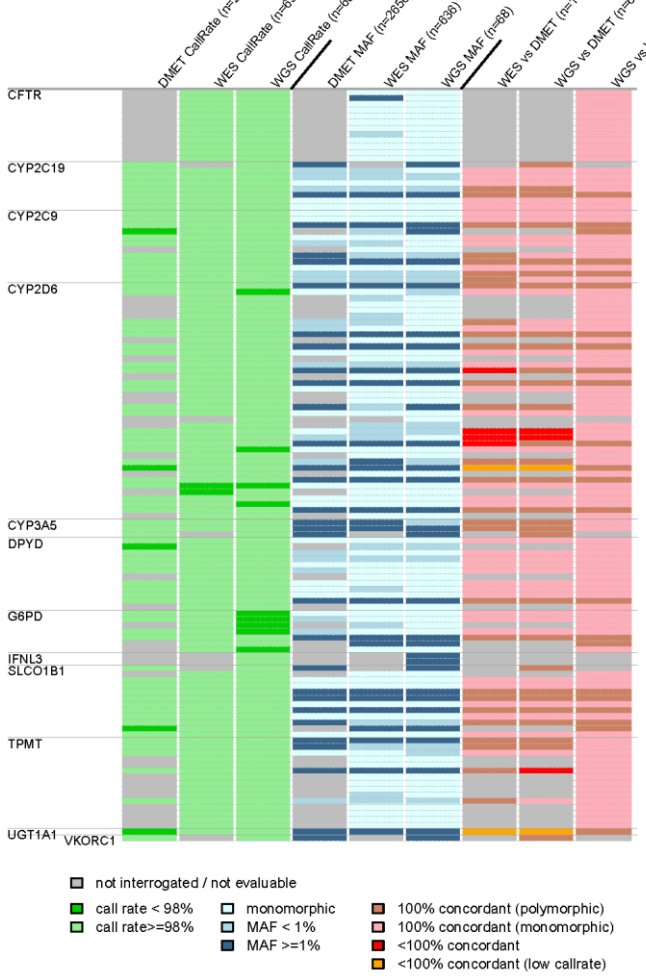

Figure 7: Pharmacogenetic test results generated as part of PG4KDS protocol (DMET) are highly concordant with test results generated via whole exome sequencing (WES) and via whole genome sequencing (WGS) (Yang W et al, Clin Pharm Ther 2016)

An inpatient census of approximately 55 patients per day requires more than 2,100 dispensed doses per day. Nutrition support, pharmacokinetic, and pharmacogenetic consults, (Figure 7) and routine

medication reconciliation at discharge require direct pharmacist involvement in patient care. Patients requiring intravenous therapy while outside the hospital are managed through provision of therapy by the St. Jude Home Infusion Pharmacy. This service, initiated in early spring of 2011, was recognized by a Joint Commission surveyor as exhibiting several "best practices" and having no recommendations for improvement during multiple TJC surveys. This service is now providing more than 340 doses per day, and is caring for all St. Jude patients in the immediate service region. At St. Jude, we provide the very best professional environment for pharmacists (Figure 8) – one that supports growth and achievement of professional goals. Clinical Staff Pharmacists work from both centralized and decentralized settings to collaborate with clinical providers in patient care. Clinical Research Pharmacists, Informatics Pharmacists, and pharmacist leaders in medication outcomes and medication safety work to assure optimal system support and design to facilitate the best outcomes of patient care and clinical research. Certified Pharmacy Technicians collaborate with pharmacists to assure excellence in operational functions. A technician career ladder has been developed, and pharmacist developmental pathways provide internal opportunities for professional growth.

Professional society involvement is encouraged, and resources are dedicated to enhance professional growth. St. Jude pharmacists play an active role in the Children's Oncology Group, American College of Clinical Pharmacy, American Society of Health-System Pharmacy, and many other professional organizations.

St. Jude Pharmaceutical Services also collaborates closely with various colleges of pharmacy in providing experiential education to pharmacy students. The department is formally affiliated with the University of Tennessee (UT) College of Pharmacy, but also works with students from other colleges as they request the opportunity. Members of the department hold affiliated faculty appointments with the UT College of Pharmacy. St. Jude pharmacy personnel provide over 50 student-months of "advanced experiential" training experience, additional "introductory" experiences, and approximately 40 contact hours of classroom training for pharmacy students from various colleges of pharmacy (primarily UT).

Figure 8. Pharmacists are integral members of each of St. Jude's clinical services.

Pharmacists are integrated into each of the major clinical services at St. Jude and state-of-the-art distribution and computer support systems assure efficient, effective delivery and use of medications. Pharmaceutical Services Informatics is intimately involved in the maintenance and refinement of a complete electronic medical record with computerized prescriber order entry and clinical decision support. These same personnel lead efforts to identify and implement the best technology to ensure optimal and safe patient outcomes.

Pharmacy Specialty Residencies

Trainees at St. Jude are supported by an institutional Office of Academic Programs, whose goal is to assist our investigators and professional staff to improve the quality of experiences, training, benefits, and support for our undergraduate, graduate, professional and postdoctoral trainees. Over 300 post-doctoral trainees (post-Ph.D, M.D, and Pharm.D.) are at St. Jude, among whom are our PGY2 pharmacy specialty residents. Our PGY2 residencies in Pediatric Oncology, Medication Use Safety, and Clinical Pharmacogenomics are accredited by the American Society of Health System Pharmacists (ASHP). Further details are available on St. Jude's website (www.stjude.org/pharmacyresidency).

Figure 9. St. Jude PGY2 residents 2017-2018 (left to right): Amanda Gillispie, PharmD; Hannah Sauer, PharmD; Kristen Hughes, PharmD; Keito Hoshitsuki, PharmD

Pharmacokinetics Shared Resource (PKSR):

The Pharmacokinetics Shared Resource is part of the NCI-designated Comprehensive Cancer Center, is housed within Pharmaceutical Sciences laboratory space, is directed by Dr. Mary Relling and Dr. Kristine Crews, and provides centralized high-quality, competitively funded, peer-reviewed pharmacokinetic/pharmacodynamics research in both clinical and pre-clinical models at St. Jude. Dr. Carl Panetta is the PKSR's biomedical modeler, who leads regular PK/PD workshops at St. Jude. There are four major functions of the PKSR:

1. **Assist investigators with implementation of clinical protocols involving PK/PD studies, including assisting with study design and optimal sampling**. Implementation includes set-up of Cerner mnemonics and instructions, set-up of laboratory procedures and tracking mechanisms, communication with sponsors and investigators, refinement of PK sampling, PK nursing assistance, in-servicing of clinical departments, development of standard physician orders, building computerized laboratory tests, refining sampling and study design (see function #4 below), and development of pharmacokinetic data collection forms.
2. **Ensure efficient and proper acquisition and initial processing of biological samples for clinical PK/PD research studies (centralized receiving, initial processing, storage, and distribution)**. Processing of clinical research samples includes computerized tracking and labeling systems for acquisition, tracking, and distribution; initial centrifugation; long- and short-term storage; and distribution to other investigators within St. Jude and outside of St. Jude.
3. **Analytical assay implementation, validation, and ongoing quality control.** Analytical assay implementation includes stringent validation procedures, the guidelines for which are available in the FDA's Guidance for Industry: Bioanalytical Method Validation. Ongoing and systematic analytical quality control procedures are in place for all PK Shared Resource assays. Equipment is interfaced with state-of-the-art laboratory information management systems and biomedical modeling software.

4. **Develop and apply novel biomedical modeling.** Dr. Panetta and the department faculty assist with biomedical modeling, which has three main phases: model design, sampling strategies, and data analysis. The model design phase involves determining the most appropriate pharmacokinetic/pharmacodynamic model which adequately describes the data, considering historical and preliminary clinical data. The sampling strategies phase involves determining the most appropriate sampling times (using D-optimality methods); those that provide the most pharmacokinetic/pharmacodynamic information with the least inconvenience to the patients and staff. The data analysis phase involves determining and using the most appropriate nonlinear curve fitting techniques to best describe the data. These include maximum likelihood estimation, maximum a posteriori probability (MAP) estimation for individual results, and linear and nonlinear mixed effects modeling methods for population results.

Clinical Pharmacokinetics Laboratory

The Clinical Pharmacokinetics Laboratory (CPK lab), located in the Pharmaceutical Department, supports St. Jude's mission by providing state of the art therapeutic drug monitoring and pharmacogenetic testing that is interpreted by clinical pharmacists to assure optimal drug dosing. It is directed by Dr. Alejandro Molinelli with translational support from Dr. Kristine Crews.

The Clinical Pharmacokinetics Laboratory is certified as a high complexity laboratory by CLIA and is accredited by the College of American Pathologists. Our staff consists of licensed medical laboratory scientists. Every year the laboratory will process and analyze approximately 8900 clinical specimens and send-out another 300 to reference laboratories. The laboratory's in-house test menu includes multiple high-complexity assays ranging from therapeutic drug determinations (e.g. immunosuppressant, antifungal drugs) to glomerular filtration rate estimation using 99mTc- DTPA. Some of our resources include random access immunochemistry analyzers (e.g. Abbott Architect) and analytical instrumentation (e.g. LC-MS/MS, GC/MS, HPLC).

Most of our instruments have bidirectional interfaces with the Cerner Millennium clinical informatics system. The laboratory also handles pharmacogenetic testing for the hospital, offering genotyping results that are always accompanied by consults prepared by the clinical pharmacists or pharmacy specialty residents.

The laboratory staff and pharmacists at St. Jude work closely to provide results in a timely manner. Once a test result is obtained, the laboratory scientists alert the pharmacist, who in turn prepares a clinical consult. This close integration of care assures that our patients receive the best treatment while minimizing adverse effects from the drugs. The laboratory staff is also involved in clinical translational science projects, for which tests developed in the research laboratories are validated and incorporated into the CPK lab test menu as needed.

In addition to the samples for clinical testing, the CPK laboratory staff members also process thousands of patient research specimens a year, in support of various St. Jude research protocols, for the Pharmacokinetics Shared Resource.

2017 - 2018 Pharmaceutical Department Publications

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R. Nishii
T. Owens
M. Payton
N. Selvo
B. Smart
C. Suggs
C. Suiter
V. Stokes
Yan Wang
Yao Wang
K. Yasuda
B. Zhong

Clinical PK Lab and Pgx
A. Molinelli, PhD, PK Clin Lab Director
K. Effinger
L. Howell
S. Johns
E. McClure
E. Melton
C. Rose
C. Suggs
Kris Crews, PharmD, Lab Director
Kelly Caudle, PharmD, CPIC Proj Leader
Cyrine Haidar,PharmD, Coord-Clin, Pgx
Roseann Gammal, PharmD

Computer Specialists - Sci
Nancy Kornegay, Director, Pharm Sci Informatics
Austin Springer, Sr. DB Analyst
Andrey Matlin, DB Analyst
Colton Smith, Info Analyst
Wenjian Yang, Bio Analyst

Administrative Staff - Sciences
Carla Cook, Administrative Director
Dawn Bowen, Coord-Pharm. Sci. Admin.
April Blankenship, Admin Spec
Angela Fletcher, Admin Spec
LaTonya Summers, Admin Spec
Amy Cain, Admin Spec

Administrative Staff - Services
Camille Doty, Admin. Manager
Taneshia Buckner-Briggs, Admin Spec
Astrid Mathis, Pharmacy Billing Coordinator
Laura Todd, Pharmacy Billing Coordinator
Amanda Ayers, Administrative Assistant II

Medication Outcomes & Safety
James Hoffman, Chief Patient Safety Officer
Jennifer Robertson, Medication Outcomes & Safety Officer
Jon Burlison, Patient Safety Research Associate
Delia Carias, Coordinator, Medication Use Policy
Clay Daniels, Clin Pharm, Med Safety Informatics

Pharmaceutical Services

William Greene, PharmD, BCPS, FASHP
Chief Pharmaceutical Officer

William Humphrey, Director, Pharmacy Operations
John McCormick, Director, Clinical Pharmacy Services
Steve Pate, Director, Outpatient Pharmaceutical Services
David Aguero, Manager, Medication Services & Informatics
Wendell Cheatham, Manager, Purchasing & Inventory
Barry Williams, Manager, Inpatient Services
Cheri Wilkerson, Manager, Outpatient Pharmacy Services
Jennifer Pauley, Clinical Pharmacy Coord/Residency Program Director

Sr. Clinical Staff Pharmacists
Susan Carr, PharmD
Shane Marshall, PharmD
Monica Patel, PharmD
Gayle Westmoreland, PharmD

Clinical Pharmacy Specialists
Liz Hall, Pharm D
PJ Barker, PharmD
Allison Bragg, PharmD
Andy Christensen, PharmD
Shane Cross, PharmD
Ted Morton, PharmD
Melissa Quinn, PharmD
Hope Swanson, PharmD
Deborah Ward, PharmD
Diana Wu, PharmD

Invest. Studies Pharm
Robbin Christensen, DPh
Linda Marden, DPh
Julie Richardson, PharmD
Chris Scobey, PharmD
Camille Smith, PharmD

Specialty Infusion Nurses
Nichole Lewis, BSN, RN, CPN
Mary Reynolds, BSN, RN
Ellie Thornton, BSN, RN

Student Interns
M. Buckley
S. Duffey
K. Heintz
B. McGlaughin
P. Metcalf
S. Patel
K. Tartera
T. Verstak
R. Wilbert

Clinical Pharmacists
C. Askins
R. Bruno
J. Bryant
M. Coleman
H. Danzi
D. Ethridge
J. Evans
L. Gallimore
T. Jacobs
J. Kemper
J. Knych
C. Longserre
J. Mason
A. McCormick
T. Mills
J. Moore
T. Nason
T. Nguyen
T. Peery
J. Quackenbush
L. Schiff
K. Smith
T. Todd
D. Trone
D. Ulrich
E. Wilson
M. Wilson
C. Yeh
K. Young

Clinical Pharmacy Residents
A. Gillispie
K. Hoshitsuki
K. Hughes
H. Sauer

Pharmacy Technicians
T. Akins
D. Black
L. Bowman
R. Branum
M. Brittmon
S. Brittmon
M. Brown
T. Bryant
D. Calhoun
L. Carlton
H. Cash
R. Chapman
N. Cole
R. Connors
J. Cooper
R. Garrett
C. Greer
C. Henderson
P. Houston
A. Hunley
K. Hunter
P. Hunter
C. Johnson
D. Lewis
A. London
N. Lundy
B. Macklin
A. Martin
K. McClelland
K. McRae
E. McVey
S. Milan
C. Owens
N. Sims
T. Smith
S. Summerhill
P. Taylor
W. Taylor III
D. White
L. Wild
S. Williams

Computer Specialists – Srv
Richard Clark, Pharmicist -Clin Inf
Nousheen DeRenzo Pharmacist – Clin Inf
Bruce Girdler, Coord Ph Sys
Murad Hasan, Sr. Database Analyst
Tim Hill, Ph Inf Spec II/ 340B Coord.
Elaine King, Ph Inf Spec I
Chris Moon, Ph Inf Spec I
Alex Rodriguez, Ph Inf Spec II

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