



# DEPARTMENT OF PHARMACY & PHARMACEUTICAL SCIENCES

## Faculty:

**Full Members:** William E. Evans, PharmD (*Emeritus*); William Greene, PharmD (*Vice-Chair, Pharmaceutical Services*); Mark Leggas, PhD; James M. Hoffman, PharmD, MS; Mary V. Relling, PharmD; P. David Rogers, PharmD, PhD, (*Chair*); Erin G. Schuetz, PhD; John D. Schuetz, PhD; Clinton F. Stewart, PharmD; Jun J. Yang, PhD (*Vice-Chair, Pharmaceutical Sciences*)

**Assistant Members:** Daniel Savic, PhD; Liqin Zhu, PhD

**Instructor:** Jeffrey Rybak, PharmD, PhD

## Laboratory Directors:

Kristine R. Crews, PharmD, Mark Leggas, PhD, Alejandro Molinelli, PhD,

## Postdoctoral Fellows:

Stefanie Baril, PhD; Kashi Raj Bhattarai, PhD; Christian DeJarnette, PhD; Kaushik Dey, PhD; Carolin Escherich, PhD; Li Fan, PhD; Tomoka Gose, PhD; Shawn Lee, MD; Yizhen Li, PhD; Maud Maillard, PhD; Sabina Ranjit, PhD; Xujie (Andy) Zhao, PhD

## Pharmacy Residents:

Madison Cole, PharmD, Chad Compagner, PharmD, Katelyn Phillips, PharmD, Rachael Stone, PharmD

## Graduate Students:

Brennan Bergeron, Carlotta Bidoli, Joanne Candeo, Laura Doorley, Ashley Gray, Jianzhong Hu, Jeremy Hunt, Kyle Kauler, Joey Miller, Kumar Niloy, Satoshi Yoshimura, Jingwen Zhu.

## Informatics Staff:

Murad Hasan, Elaine King, Nancy Kornegay, Andrey Matlin, Claire Mills, Chris Moon, Ben Moore, PharmD, Ben McKinley, Carl Panetta, PhD, Wenjian Yang, PhD

## Staff Scientists:

Kathy Barker, PhD, Yu Fukuda, PhD, John Lynch, PhD, Kamalika Mukherjee, PhD, Ana Oliveira Souza, PhD, Kazuto (Yaz) Yasuda, PhD

## Pharmacy Leadership:

David Aguero, PharmD; Cindy Brasher, PharmD, MS; Delia Carias, PharmD; Kelly Caudle, PharmD, PhD; Wendell Cheatham, BS Pharm; Cyrine Haidar, PharmD; William Humphrey, BS Pharmacy, MS, MBA; John McCormick, PharmD; Steve Pate, DPh; Jennifer Pauley, PharmD; Jennifer Robertson, PharmD; Cheri Wilkerson, PharmD; Barry Williams, BS Pharm

## Clinical Pharmacy Specialists:

PJ Barker, PharmD; Melissa Bourque, PharmD; Allison Bragg, PharmD; Andy Christensen, PharmD; Shane Cross, PharmD; Tim Jacobs, PharmD; Ted Morton, PharmD; Linda Schiff, PharmD; Joe Sciasci, PharmD; Hope Swanson, PharmD; Deni Trone, PharmD; Deborah Ward, PharmD; Diana Wu, PharmD

## Pharmacists:

Chris Askins, PharmD; Amy Bass, PharmD; Robert Bruno, PharmD; Susan Carr, PharmD; Richard Clark, PharmD; Clay Daniels, PharmD, PhD; Nousheen DeRenzo, PharmD; Ryan Duncan, PharmD; Nicole Edwards-Durden, PharmD; Maureen Esposito, PharmD; Debra Ethridge, PharmD; Joseph Evans, PharmD; Kelsey Finnell-Smith, PharmD; Liz Gallimore, PharmD; Timothy Howze, PharmD; Kristen Hughes, PharmD; Nevonda Jackson, PharmD; Jennifer Kemper, PharmD; Jenny Knych, PharmD; Chuck Longserre, PharmD; Shane Marshall, PharmD; Jennifer Mason, PharmD; Anne McCormick, BS Pharm; Tommy Mills, PharmD; Ben Moore, PharmD; Heather Morgan, PharmD; Heather Mullins, PharmD; Tiffany Nason, PharmD; Monica Patel, PharmD; Trina Peery, PharmD; Jackie Quackenbush, BS Pharm.; Julie Richardson, PharmD; Robert Rutschman, PharmD; Chris Scobey, PharmD; Camille Smith, PharmD; Kevin Smith, PharmD; Tabettha Todd, PharmD; Dagny Ulrich, PharmD; Gayle Westmoreland, BS Pharm.; Curtis Yeh, PharmD; Keith Young, BS Pharm; RJ Zarkani, PharmD

# BY THE NUMBERS

**13**

faculty members

**35**

PhD scientists

**13**

post-doctoral fellows

**7**

graduate students

**72**

pharmacists

**25**

BPS certified  
pharmacists

**4**

PGY2 pharmacy  
residents

**2**

National Academy  
of Medicine  
members

**7**

Fellows of the  
American College  
of Clinical  
Pharmacy

**4**

Fellows of the  
American Society  
of Health-System  
Pharmacists

**1**

Fellow of the  
American Society  
for Pharmacology  
& Experimental  
Therapeutics

**2**

Fellows of the  
American  
Association of  
Pharmaceutical  
Scientists

**2**

Fellows of the  
American  
Association for the  
Advancement of  
Science

**90**

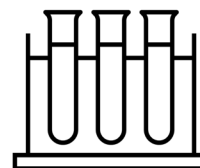
total publications

**10.8**

median journal  
impact factor

**31**

publications in journals with  
an impact factor of >10



**\$6,389,886**

grant funding/active extramural funding

**\$5,653,287**

total active NIH funding



# The overall mission of the Department of Pharmacy & Pharmaceutical Sciences

## OVERVIEW

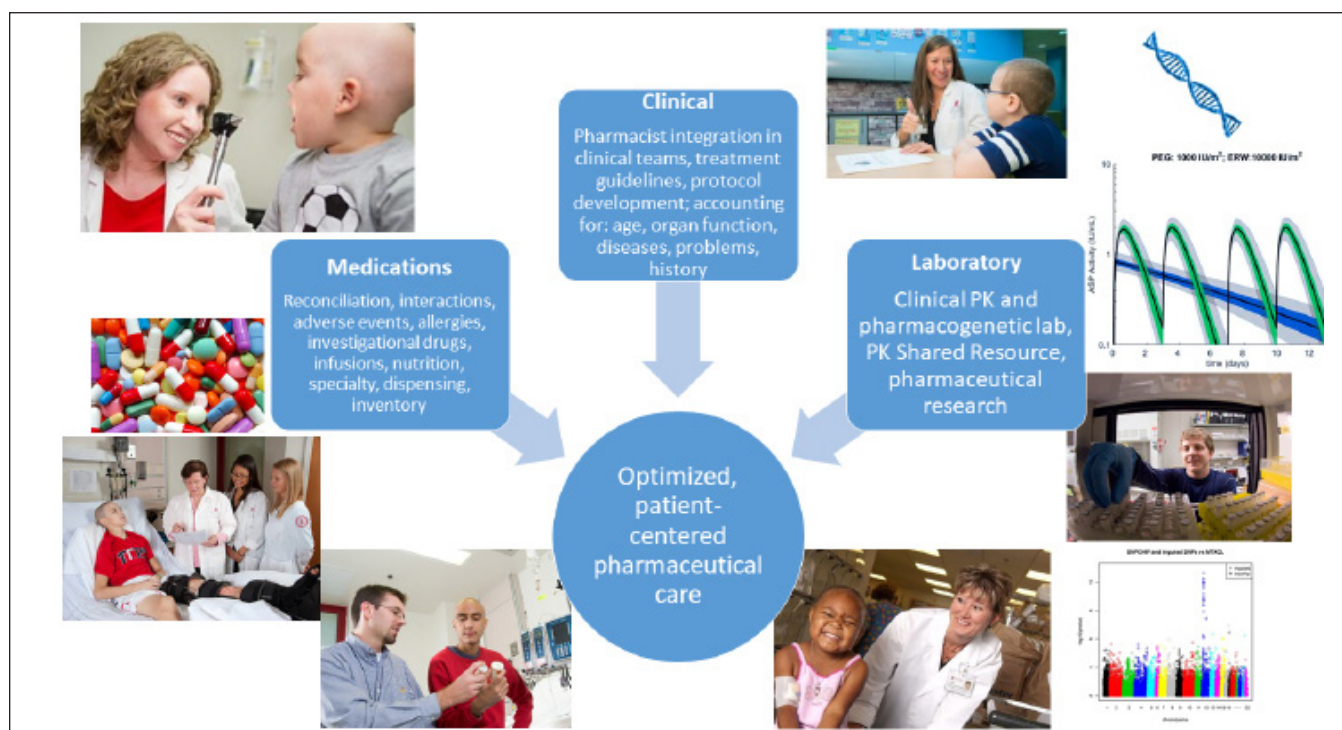
is to discover the basis for inter-individual differences in response to medications, to translate research findings to improve treatment outcomes, and to provide the best and most comprehensive pharmaceutical care for our patients. The department comprises the Division of Pharmaceutical Sciences (with a primary mission of research) and the Division of Pharmaceutical Services (with a primary mission of clinical care). Both research and treatment are highly intertwined at St. Jude Children's Research Hospital, and this integration exists within other academic departments at St. Jude 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 St. Jude since it was established in 1962 and facilitates the success of our institution.

Our vision is to be a premier academic pharmacy and pharmaceutical sciences department, encompassing clinical pharmaceutical care and research, with special expertise in 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 suboptimal use of medications. Our goal is to elucidate the biological basis of inter-individual differences in pharmacologic response, and to translate our findings into more rational therapeutics and improving patient care.

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 non-genetic factors (e.g., drug interactions, host organ function and maturity, disease severity, adherence to therapy). Anti-infective therapy can further be influenced by genetic variability in the infecting pathogen that can result in anti-infective tolerance or resistance.

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



**Figure.** 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 also making discoveries with implications outside of St. Jude.





Stefanie Baril, PhD



Kashi Raj Bhattarai, PhD



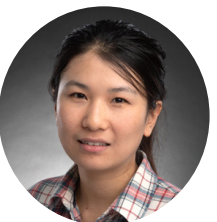
Christian Delamette, PhD



Kaushik Dey, PhD



Carolin Escherich, PhD



Li Fan, PhD



Keito Hoshitsuki, PharmD, PhD



Shawn Lee, MD



Yizhen Li, PhD



Maud Maillard, PhD



Sabina Ranjit, PhD



Cheng Tian, PhD



Xujie (Andy) Zhao, PhD

pharmacokinetics, and pharmacodynamics to identify genetic determinants of drug effects, with the long-term goal of optimizing therapy for individual patients. The Department has twelve faculty members, 15-25 post-doctoral fellows and residents (see page 28), 10-20 undergraduate and graduate students, over 72 pharmacists (25 board certified), and over 125 full time staff members working as computing experts, research nurses, technical, laboratory, administrative, and clinical staff.

The department is led by Dr. David Rogers who serves as chair, and Drs. Jun Yang and Bill Greene who serve as vice-chair of the Divisions of Pharmaceutical Sciences and Pharmaceutical Services, respectively.

The department is supported in part by grants from industry, foundations, and the National Institutes of Health. 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. The Division of Pharmaceutical Sciences occupies over 15,000 sq. ft. of contiguous state-of-the-art equipped laboratory and office space, and the Division of 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 and monthly seminars that are open to the entire institution. As well as multiple laboratory-and-services specific-meetings, webinars with national and international colleagues, and regular pharmacogenomics meetings.

**Figure.** Postdoctoral fellows in the Division of Pharmaceutical Sciences

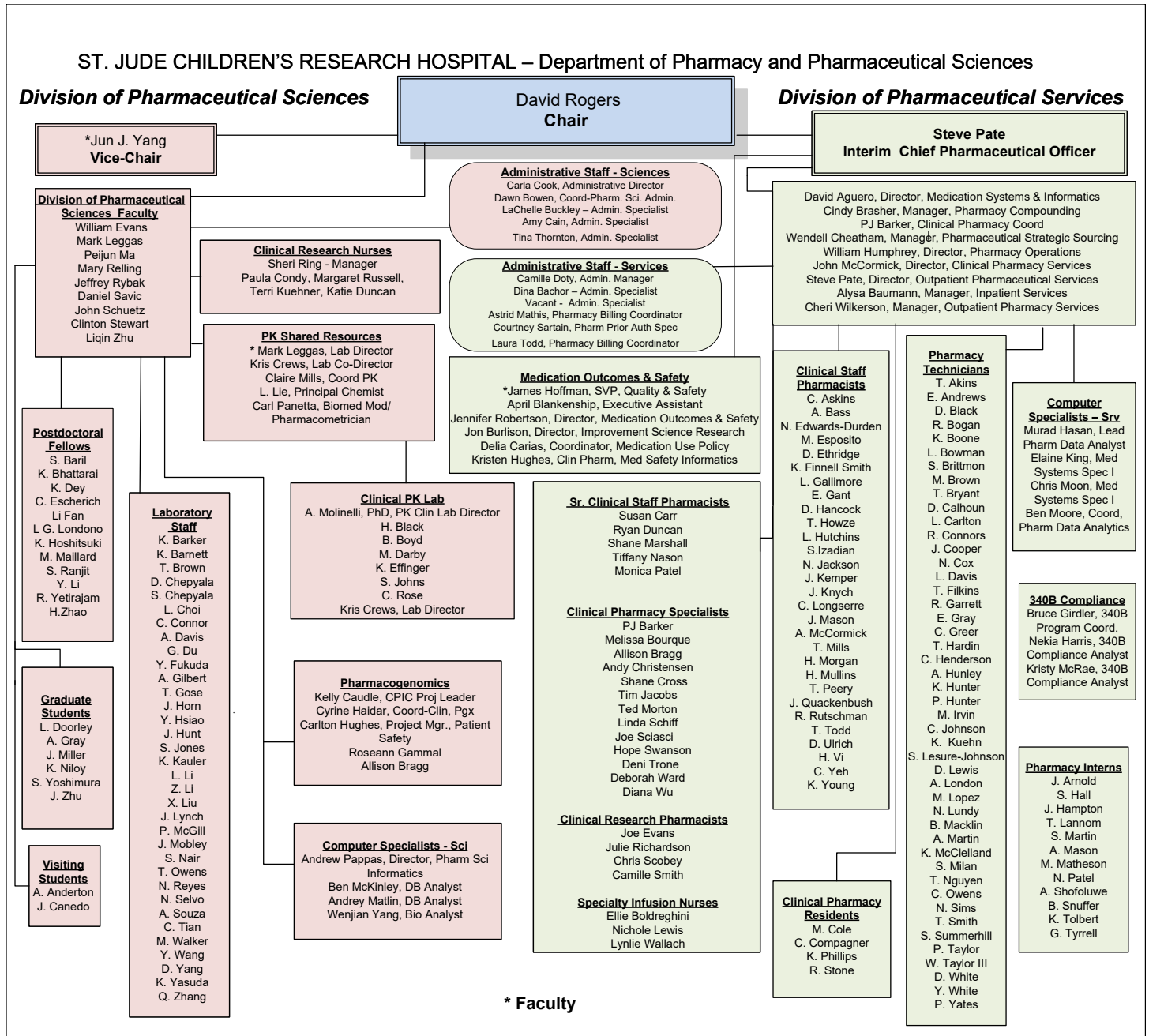
## ABOUT THE CHAIR

Dr. David Rogers serves as Chair of the Department of Pharmacy and Pharmaceutical Sciences at St. Jude and holds the St. Jude Endowed Chair in Pharmaceutical Sciences. He received his Pharm.D. from the University of Tennessee, and M.S. and Ph.D. (in Microbiology and Immunology) from the University of Mississippi. He completed residency in pharmacy practice (PGY1) at the Regional Medical Center, Memphis, and residency (PGY2) and clinical fellowship in infectious diseases pharmacy practice at the University of Mississippi Medical Center. Prior to joining the faculty at St. Jude, he was Professor of Clinical Pharmacy and Translational Science at the University of Tennessee College of Pharmacy. There he also held the First Tennessee Endowed Chair of Excellence in Clinical Pharmacy, served at various times as Vice Chair of the Department of Clinical Pharmacy and Translational Science, Associate Dean for Clinical and Translational Research, and Director of the UTHSC Center of Excellence for Pediatric Experimental Therapeutics. He is an elected Fellow of the American College of Clinical Pharmacy (ACCP) and the American Academy of Microbiology. He has served on the Board of Trustees for the ACCP Research Institute and the Board of Directors for the Society of Infectious Diseases Pharmacists. He recently completed a 6-year term as a member of the NIH Drug Discovery and Mechanisms of Antimicrobial Resistance (DDR) Study Section and currently serves

on the Board of Trustees of the ACCP Foundation and has been appointed as an Ex Officio Member of the National Academies Forum on Antimicrobial Threats. For over two decades his research program has focused on improving antifungal pharmacotherapy through the study of how pathogenic fungi respond and develop resistance to antifungal agents. He has authored over 330 publications and scientific abstracts, has received funding from foundations, industry, and the NIH, and currently serves as PI for several NIH R01 grants. In 2021 he received both the ACCP Russell R. Miller Award and the ACCP Therapeutic Frontiers



# ORGANIZATIONAL CHART

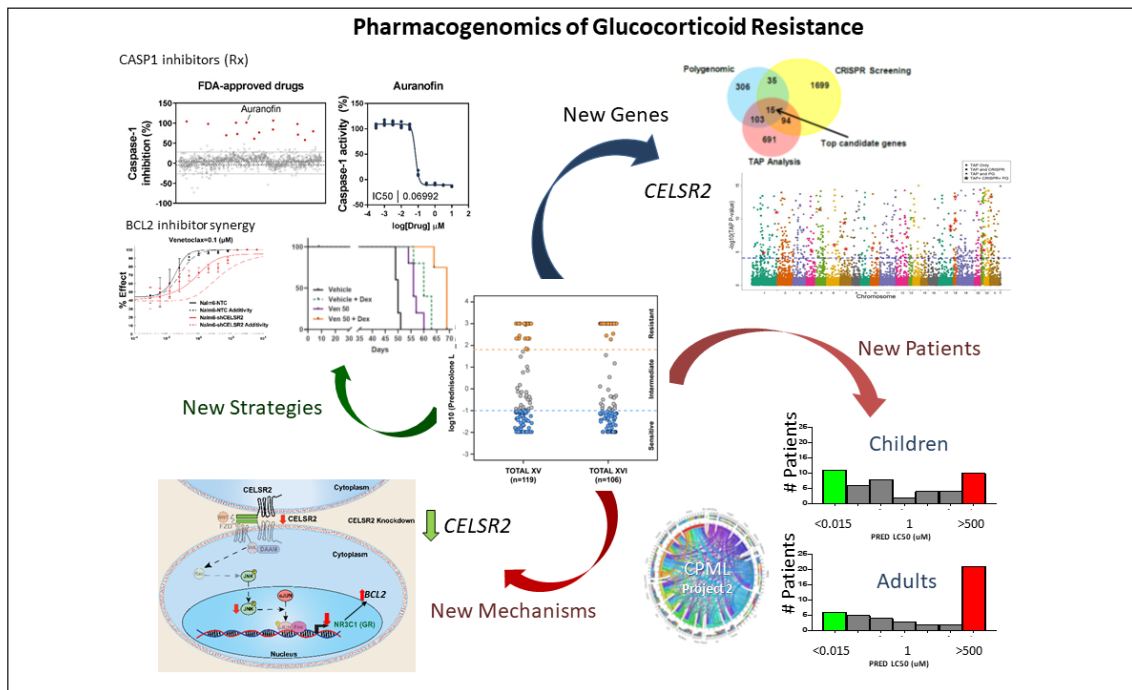


# WILLIAM E. EVANS, PHARMD EMERITUS FACULTY



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; 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 integrative 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 CpG-methylation analyses and whole exome/genome sequencing of patient cohorts whose leukemia cells have been evaluated for drug sensitivity and clinical response on prospective clinical trials. Ongoing studies are investigating genes that the lab has linked with resistance to antileukemic agents (*Holleman, NEJM 2004; Lugthart, Cancer Cell 2005; Paugh, Nature Genet 2015; Autry, Nature Cancer 2020*), and genes linked to the disposition (*Kager, JCI 2005; Lopez JCI 2020*) or pharmacologic targets (*Lee et al, Nat. Med. 2023, Diouf, JAMA 2015; Paugh, Nat Genet 2015, Autry Nature Cancer 2020*) of antileukemic agents, as well as the influence of somatic and karyotypic abnormalities on genotype-phenotype concordance (*Cheng, Nature Genet 2005; Diouf et al, Nature Med 2011*). Having previously identified high CASP1/NLRP3 expression as a mediator of glucocorticoid

resistance (*Paugh, Nat Genet, 2015*), we are currently targeting this mechanism as a strategy to sensitize cells to glucocorticoids (GC). A high-throughput screen has identified an FDA approved medication (auranofin) that is able to block CASP1 activity and restore expression of the glucocorticoid receptor (GR) in ALL cells. Our ongoing research is directed at determining if combinatorial therapies with auranofin and glucocorticoids can prevent GR degradation by CASP1 and enhance leukemia cell response to glucocorticoids in ex vivo and in vivo models and in primary ALL cells from patients. The Evans lab officially closed in 2021 and is no longer taking students or post-doctoral trainees. The lab and its collaborators continue the analyses and reporting of data that were generated over the last several years, toward advancing its goals of improving the safety and efficacy of medications used to treat children with cancer.



**Figure.** In work supported by the NIH funded Center for Precision Medicine in Leukemia, we have initially focused on identifying mechanisms by which primary acute lymphoblastic leukemia (ALL) cells are resistant to chemotherapy, at the time of initial diagnosis (i.e., de novo resistance). Our initial research has focused on glucocorticoids (GC), which are a mainstay of curative combination chemotherapy for every child with ALL. This has revealed two novel mechanisms of GC resistance; (1) overexpression of CASP1 and its activator NLRP3 in ALL cells, due to somatic hypomethylation of their promoters, leading to caspase 1 cleavage of the glucocorticoid receptor (GR), as reported in Paugh et al, Nature Genetics, 2015., and (2) more recently, we have discovered that low expression of the G-protein coupled receptor, CELRS2, leads to glucocorticoid resistance, due to down-regulations of GC expression and up-regulation of BCL2 after GC treatment (Autry et al, Nature Cancer, 2020). Our work has also focused on identification of strategies to mitigate these new mechanisms of resistance, which can be achieved by concomitant treatment with the BCL2 inhibitor venetoclax for GC resistance due to low CELRS2 expression. In a high throughput screen of FDA approved medications, we have more recently found that auranofin can inhibit Caspase 1 in ALL cells, and thereby mitigate GC resistance from this mechanism (unpublished data). Because these two mechanisms are found in approximately 23% and 40% of GC resistant ALL, they represent common mechanisms for GC resistance in children with newly diagnosed ALL.



# WILLIAM GREENE, PHARM.D

## MEMBER & VICE-CHAIR

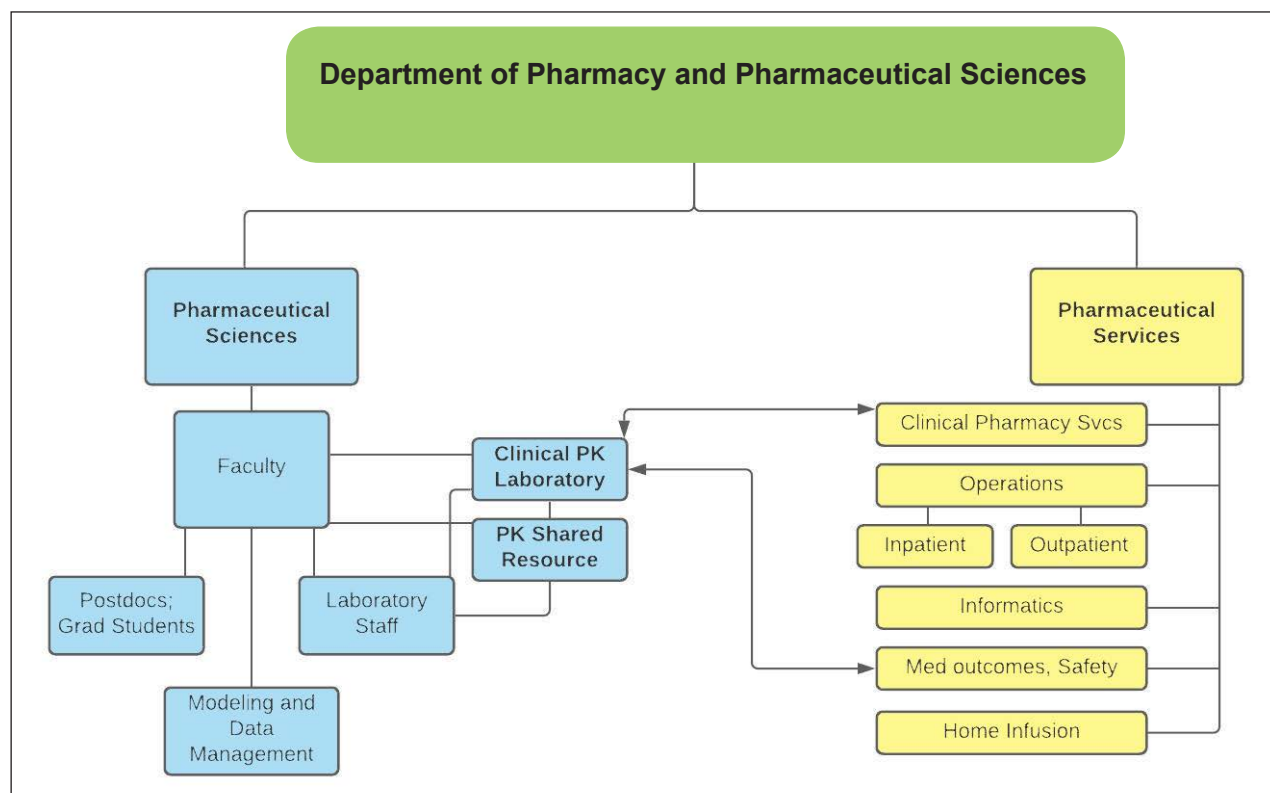
### CHIEF PHARMACEUTICAL OFFICER

### DIVISION OF PHARMACEUTICAL SERVICES



Dr. William Greene joined Pharmaceutical Services as Chief Pharmaceutical Officer in August 2007. He has had a long career as a clinical pharmacy practitioner and leader in development of drug policy in hospital-based practice. His 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. His interests lie in infectious diseases, pharmacokinetics, performance improvement, and medication safety.

As the senior leader of Pharmaceutical Services, it is his 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 improvement science 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. Dr. Greene currently retains a faculty appointment with the University of Tennessee College of Pharmacy (Professor, Affiliated), and is active in national and state professional organizations (NCCN Cancer Center Pharmacy Directors Forum, American College of Clinical Pharmacy, American Society of Health Systems Pharmacists, and Tennessee Society of Health-Systems Pharmacists/Tennessee Pharmacists Association). He is a Fellow of the American College of Clinical Pharmacy and of the American Society of Health-System Pharmacists.



**Figure.** Department of Pharmacy and Pharmaceutical Sciences

# JAMES M. HOFFMAN, PHARM.D, MS

## MEMBER

## SENIOR VICE PRESIDENT,

## QUALITY AND SAFETY



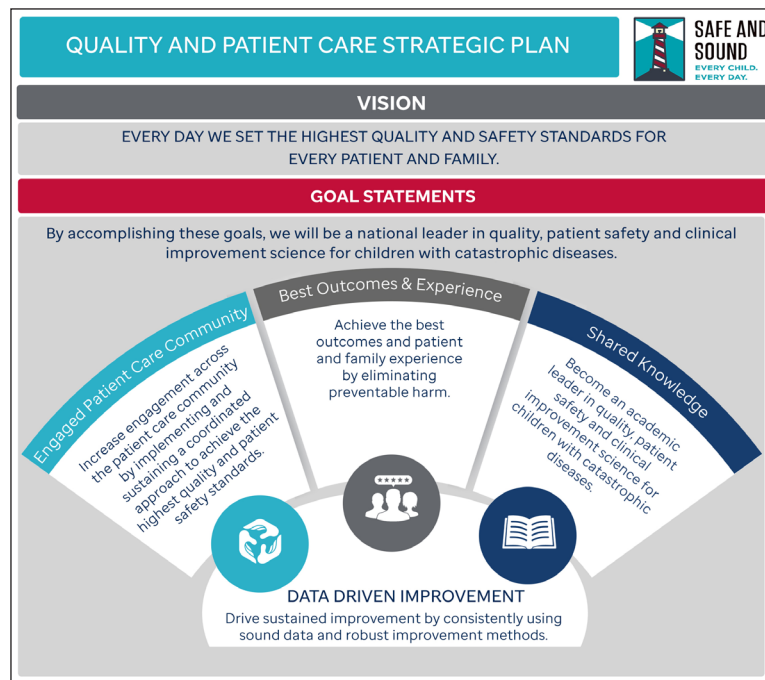
Since joining the Department of Pharmaceutical Sciences in 2004, Dr. Hoffman has focused on evaluating and improving complex medication use systems. Since 2015, he has provided oversight and leadership for patient safety as the hospital's Chief Patient Safety Officer within the Office of Quality and Patient Care.

He focuses on refining existing tools and identifying new means of patient safety event detection, assessing and improving patient safety culture, and developing and improving clinical decision support. At St. Jude, he has been involved in efforts related to all these areas, and he has extensive experience leading change across St. Jude. For example, he recently guided St. Jude's efforts to improve handoffs across multiple areas, including adapting I-PASS to be used by a range of disciplines in various handoff scenarios (*Blazin et al Ped Qual Saf 2020*).

Dr. Hoffman was a core member of the team that created the [St. Jude Safe and Sound](#) strategic plan, and he is particularly focused on helping St. Jude become an academic leader in quality, patient safety, and improvement science for children with catastrophic diseases. Two 2019 publications in

Pediatrics illustrate Dr. Hoffman's academic leadership for improvement science. One focused on improving [medication alerts](#) at St. Jude (*Daniels et al Pediatrics 2019*) and the other identified [research priorities for pediatric patient safety](#) (*Hoffman et al Pediatrics 2019*).

Through work at St. Jude (PG4KDS [www.stjude.org/pg4kds](http://www.stjude.org/pg4kds)) and nationally through the NIH funded Clinical Pharmacogenetic Implementation Consortium (CPIC <https://cpicpgx.org>), he is devoted to implementing pharmacogenetics as a patient safety strategy. Through these efforts he works to implement research discoveries in pharmacogenomics into the clinic through the development and dissemination of model practices and clinical practice guidelines. He has experience developing and refining clinical decision support for pharmacogenomics in electronic health records (reviewed in [Annual Reviews of Biomedical Data Science in 2020](#)).



**Figure.** Vision for Quality & Patient Care at St. Jude

# MARK LEGGAS, PHD MEMBER

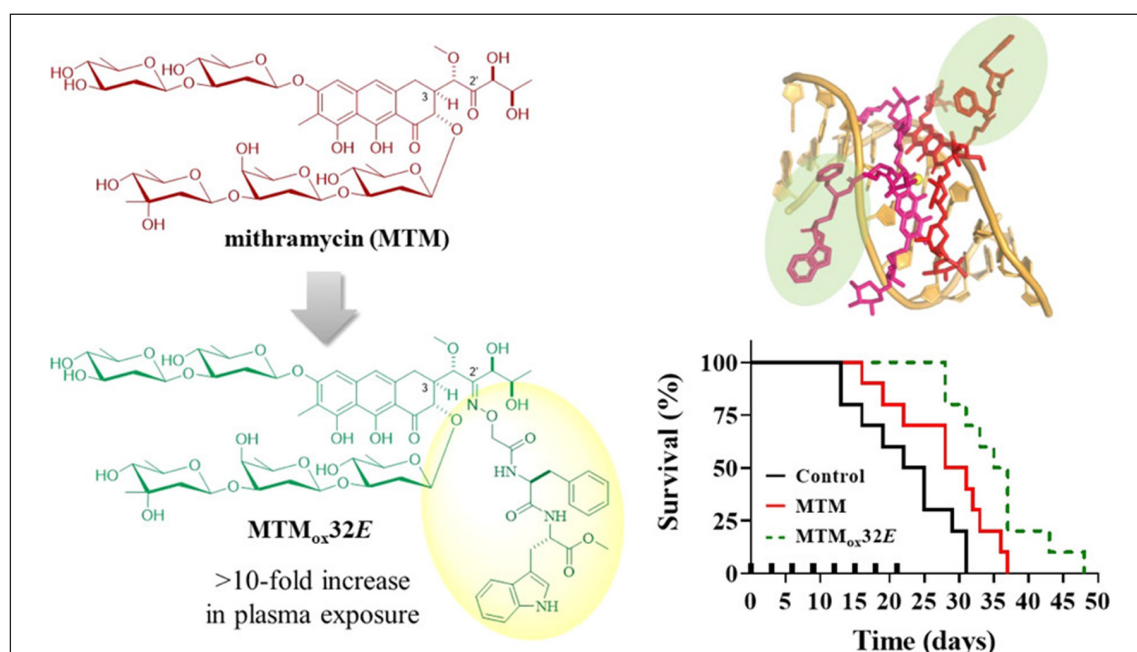


Dr. Mark Leggas joined the St. Jude Faculty in 2022 and is a Member of the Department of Pharmacy and Pharmaceutical Sciences and the Director of the Pharmacokinetic Shared Resource. The Leggas lab has a long-standing effort in translational pharmacology to optimize the clinical use of existing drugs or new drug candidates. Most recently, the lab has been awarded NCI funds to develop a new targeted therapy for Ewing Sarcoma (R01CA243529) and NIDA funding to assess the utility of a non-opioid medication to treat neonates physically dependent on opioids (R01DA043519).

The Ewing Sarcoma project is centered around using semi-synthetically modified mithramycin analogs (see figure), which have been shown to interfere with the oncogenic transcription factor responsible for Ewing Sarcoma growth. This is significant because this oncogenic transcription factor (i.e., EWS-FLI1) is recognized as the Achilles heel of Ewing Sarcoma, but efforts to develop treatments that interfere with its function have not succeeded. Currently, several analogs are progressing through preclinical evaluation and, if successful, will transition to the NCI Experimental Therapeutics program to complete all the preclinical evaluations required for entry into the clinic.

The NIDA project is centered around a randomized controlled clinical trial that evaluated the use of clonidine, an alpha-2 adrenoceptor agonist, in comparison to morphine for the treatment of neonates who are born physically dependent on opioids due to prenatal exposure. These studies are important because morphine use is detrimental to the developing brain and opioid treatment often exceeds two weeks. The Leggas lab is using population PK/PD to describe the exposure and response of each treatment in the neonates but also attempts to understand the sources of variability in drug exposure and response to treatment through population covariate modeling that includes pharmacogenetics of genes responsible for the transport, metabolism, and pharmacological action of each drug. More ambitious efforts of the study aim to identify a biomarker of physical dependence using blood metabolomics and the effect of each treatment on the development of gut dysbiosis as a marker of short-term outcomes.

Future studies in the Leggas laboratory will focus on the “pharmacology” of CAR T-cell therapies and how concomitant drug treatment and host physiology may affect the in-vivo expansion, persistence, and antitumor activity of engineered immune cells. Our approach will use metabolomic, lipidomic, and proteomic profiling to “metabotype” patients and identify molecular phenotypes that influence CAR T-cell disposition and activity. We chose to focus on the metabolome because we hypothesized that small endogenous molecules and proteins might play a role in CAR T-cell phenotype through cell surface interactions and signaling.



**Figure.** Abstract summary of J. Med. Chem. 2020, 63, 22, 14067-14086. Mithramycin analogs with substitutions in the 3-side chain via oxime chemistry yield analogs that bind to the minor groove of DNA as Mg+2 complexed dimers. These molecules have favorable pharmacokinetic profiles with lower clearance and lower toxicity, as compared to mithramycin and they display better anti-tumor efficacy.

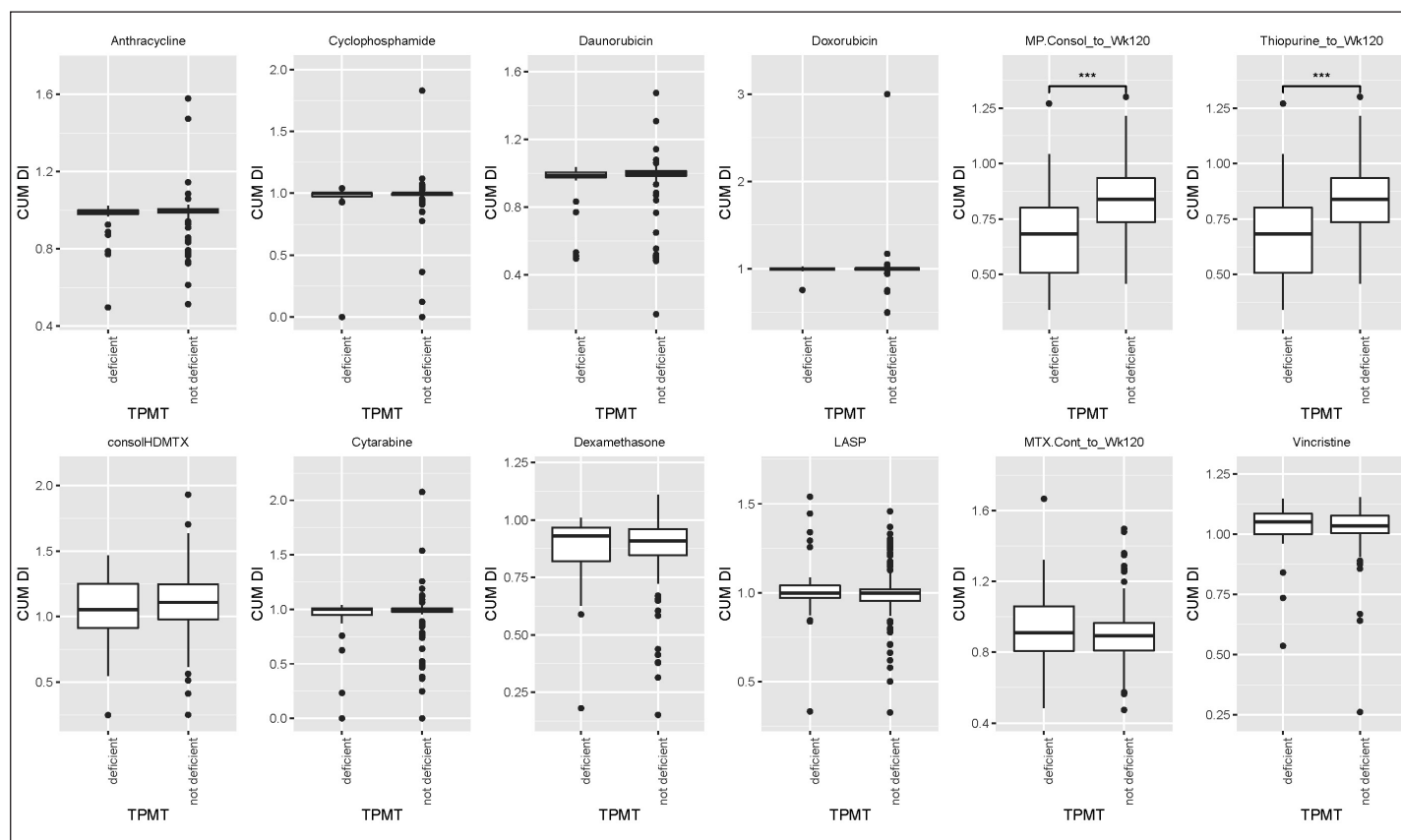


# MARY V. RELING, PHARM D MEMBER



Dr. Mary Relling has been a faculty member in the Department of Pharmaceutical Sciences at St. Jude since 1988 and served as chair of the department from 2003 to 2020. The majority of her discovery research efforts has 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. The Relling Lab conducted a major analysis of the importance of dosages and dose intensity of all drugs used to treat ALL over the past 20 years (Karol *et al*, *Haematologica*, 2021). This allowed a demonstration, for the first time, that the practice of using precision medicine approaches to tailor mercaptopurine dosages based on the genetic polymorphism in thiopurine methyltransferase (TPMT) permits uncompromised dosing of all other ALL drugs. We continue to incorporate pharmacogenetically based dosage adjustments in our ALL trials, and for all children at St. Jude via a clinical protocol, PG4KDS ([www.stjude.org/pg4kds](http://www.stjude.org/pg4kds)), which has been in place since 2011 and is now led by Dr. Cyrine Haidar.

Since moving to part-time status at the start of 2021, Dr. Relling has concentrated her efforts on facilitating clinical implementation of preemptive germline pharmacogenetic testing. She continues to assist Dr. Kelly Caudle (St. Jude) and colleagues at Stanford in their efforts to lead the international group, the Clinical Pharmacogenetics Implementation Consortium (CPIC®, [www.cpicpgx.org](http://www.cpicpgx.org)) (Caudle *et al Clinical Pharmacol Ther* 2020), an NIH-supported genomics resource. CPIC staff help lead efforts to create and curate gene/drug pair CPIC prescribing guidelines. St. Jude played a leading role in many recent CPIC guidelines (Crews *et al Clinical Pharmacol Ther* 2021; Theken *et al Clinical Pharmacol Ther* 2020; Karnes *et al Clinical Pharmacol Ther* 2021; McDermott *et al Clinical Pharmacol Ther* 2021). Our recent update of the CPIC G6PD guideline has major implications for use of commonly used medications such as trimethoprim/sulfamethoxazole, which is no longer considered a high-risk drug in those with G6PD deficiency (Gammal *et al Clinical Pharmacol Ther* 2022).



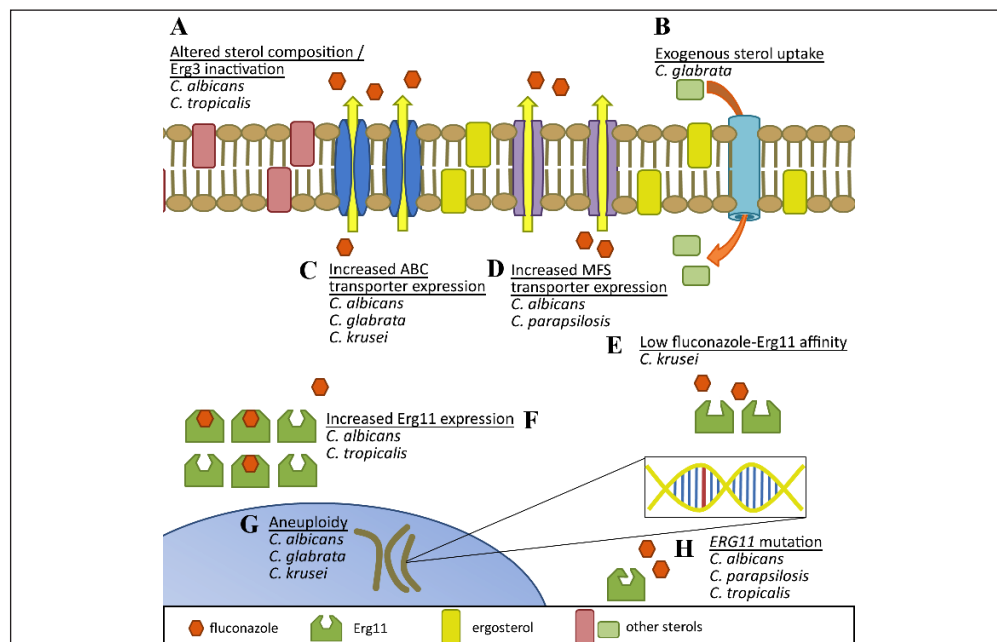
**Figure.** Depicted are the cumulative dose intensities (CUM DI) for each ALL drug in patients who were either poor or intermediate metabolizers of TPMT (deficient) vs those who had no genetic defect in TPMT (not deficient), shown for Total 15, low-risk arm. The only significant \*\*\* compromises to dosing were for thiopurines (mercaptopurine or MP or any thiopurine), which was the intended result.

# DAVID ROGERS, PHARMD, PHD MEMBER AND CHAIR ST. JUDE ENDOWED CHAIR IN PHARMACEUTICAL SCIENCES



The overarching goal of the Rogers lab is to improve the safety and efficacy of antifungal pharmacotherapy. Treatment of invasive fungal infections is limited to only three antifungal classes, each with significant shortcomings. Moreover, resistance to these antifungals has become a major clinical concern that threatens the utility of many front-line therapies. It must also be noted that very few new antifungal drug classes are on the near horizon. Novel strategies are therefore urgently needed to preserve, improve, and expand the current antifungal armamentarium. For two decades our primary focus has been on understanding the molecular and cellular basis of resistance to the triazole class of antifungal agents in pathogenic fungi. Our work exploring the transcriptional and proteomic profiles of the response to antifungals in *Candida albicans* led to the discovery of general and specific responses, some of which aligned with antifungal mechanism of action, and gave insight into factors that influence antifungal susceptibility (Liu, AAC 2005, Hoehamer, AAC 2010). We used similar approaches for analysis of azole antifungal resistance in clinical isolates of *Candida* species (Rogers and Barker, AAC 2003), which led to our discovery that activating mutations in genes encoding the transcription factors Mrr1 (Morschhäuser, PLoS Pathogens 2007) and Upc2 (Dunkel, Eukaryot Cell 2008, Flowers, Eukaryot Cell 2012) in *C. albicans* and Pdr1 (Vermitsky, Mol Micro 2006, Caudle, Eukaryot Cell 2011) in *C. glabrata* lead to overexpression of efflux pumps and the triazole target enzyme (Erg11) in clinical isolates.

More recently we have found that the transcription factor Upc2A in *C. glabrata* plays a central role in fluconazole susceptibility and are exploring the Upc2A pathway for opportunities to enhance activity of this antifungal agent against this otherwise fluconazole-resistant pathogen (Whaley, AAC 2014, Vu, PLoS Genet, 2021). We have begun to map the genomes of triazole resistant clinical isolates of *Aspergillus fumigatus* and have discovered that mutations in the region encoding the sterol sensing domain of HMG-CoA reductase are a novel driver of triazole resistance in this mold (Rybak, mBio 2019). By mapping the genomes of antifungal resistant isolates of *C. auris*, we have recently found that activating mutations in the gene encoding the transcription factor Tac1b is a major driver of fluconazole resistance (Rybak, mBio 2020), whereas mutations in ERG6, encoding sterol methyltransferase, represents the first identified mechanism of clinical resistance to amphotericin B in this emerging fungal pathogen (Rybak, Clin Microbiol Infect 2022).



**Figure.** Comparison of documented fluconazole resistance mechanisms in *Candida* species. A) Erg3 inactivation results in utilization of alternative sterols in the yeast membrane. B) Uptake of exogenous sterols helps circumvent endogenous sterol production inhibition by fluconazole. Increased production of both C) ATP-binding cassette efflux pumps and D) major facilitator superfamily transporters reduce intracellular accumulation of azoles. E) Inherently low affinity of fluconazole binding to species-specific Erg11 may decrease fluconazole's potential to inhibit the protein. F) Increased expression of Erg11 protein can help overcome azole activity and G) aneuploidy may promote genetic adaptation to azole exposure. H) Mutations in ERG11 can also result in proteins with reduced affinity for fluconazole binding.

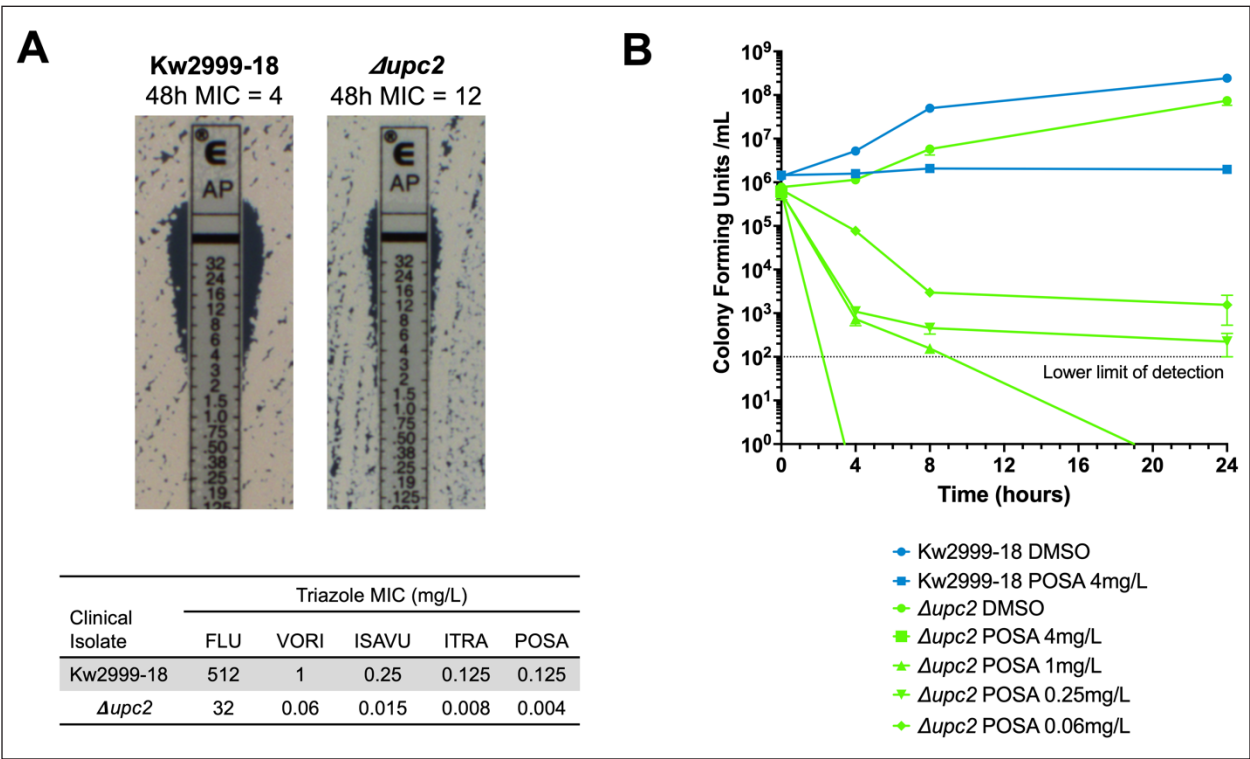
# JEFFREY RYBAK, PHARM.D, PH.D INSTRUCTOR



Dr. Jeffrey Rybak joined the faculty of the Department of Pharmaceutical Sciences at St. Jude Children's Research Hospital as an Instructor in September of 2020. Previously, his research focused on the discovery of the molecular mechanisms underpinning antifungal resistance among challenging fungal pathogens such as *Aspergillus fumigatus* and *Candida auris*. Employing whole genome and transcriptome sequencing, *in vitro* evolution studies, and targeted allelic replacement, we revealed mutations in the *A. fumigatus* HMG-CoA reductase gene, *hmg1*, and the *C. auris* zinc-cluster transcription factor gene, *TAC1B*, as widespread genetic determinants of clinical triazole antifungal resistance (Rybak et al. mBio 2019, Rybak et al. mBio 2020).

Dr. Rybak's current research program focuses on the advancement of the treatment of invasive fungal infections by developing new therapeutic strategies to overcome difficult-to-treat fungal pathogens. In pursuit of this objective, the Rybak lab has developed the *C. auris* optimized Episomal Plasmid Induced Cas9 (EPIC) system, capable of single nucleotide-editing, and used this system to interrogate the role of the fungal-specific zinc-cluster transcription factors (ZCF) in regulating the response to antifungal-induced stress in *C. auris*. We have shown that targeted disruption of one of these ZCF

genes, *UPC2*, results in decreased resistance to triazole antifungals and increased resistance to amphotericin B. Furthermore, we have observed that while triazoles are conventionally limited to fungistatic activity against species of *Candida*, disruption of *C. auris* *UPC2* conferred rapid fungicidal activity to the triazole agents at pharmacologically achievable concentrations. Our ongoing studies seek to characterize the *C. auris* *UPC2* regulatory network and to reveal molecular weak-points which can be targeted to restore and enhance the activity of the triazoles and amphotericin B. In addition to his benchtop research, Dr. Rybak is also a member of the Antimicrobial Utilization and Improvement Committee (AUIC) and co-authored the updated St. Jude Antifungal Utilization Guidelines.



**Figure.** *Candida auris*-optimized Episomal Plasmid Induced Cas9 (EPIC) system reveals the impact of genetic ablation of *UPC2* on *C. auris* triazole and amphotericin B susceptibility. **A**) Loss of *UPC2* results in increased amphotericin B (AMB) resistance as determined by test strip diffusion assay at 48 hours and reduced triazole (FLU: fluconazole; VORI: voriconazole; ISAVU: isavuconazole; ITRA: itraconazole; POSA: posaconazole) minimum inhibitory concentrations (MIC) as determined by broth microdilution at 24 hours **B**) Posaconazole, at pharmacologically relevant concentrations, exhibits a rapid fungicidal effect ( $>3 \log_{10}$  reduction in colony forming units [CFU]) against the  $\Delta upc2$  strain in time-kill analysis (DMSO: dimethyl sulfoxide solvent control)



# ERIN G. SCHUETZ, PHD MEMBER



The E. Schuetz lab works on molecular mechanisms regulating drug metabolism and transport genes, and pharmacogenomics discovery of genomic variants important for interpatient variability in response to medications metabolized and transported by these genes because there is still unexplained unpredictability in host response to and toxicity from drug therapies that is significantly influenced by hepatic and intestinal metabolism and transport mediated drug clearance. In addition, we create novel pre-clinical screening models. We recently developed and characterized a Mrp4 (Abcc4) knockout (KO) rat because KO rats are of considerable utility for mechanistic and pharmacokinetic studies. Although detailed drug distribution experiments can be conducted in knockout mice, rats are advantageous practically and, in fact, more relevant as the most commonly used preclinical species in drug development. Abcc4/Multidrug Resistance Protein 4 (MRP4) is a plasma membrane efflux transporter of important drug substrates such as adefovir and methotrexate. MRP4 is expressed in multiple tissues including kidney, blood-brain barrier, liver and platelets. The laboratory of Dr. John Schuetz had previously shown that the absence of mouse platelet Mrp4 disrupts normal platelet aggregation (Cheepala *et al.*, *Blood*, 2015). Immunohistochemical and immunoblot analysis confirmed

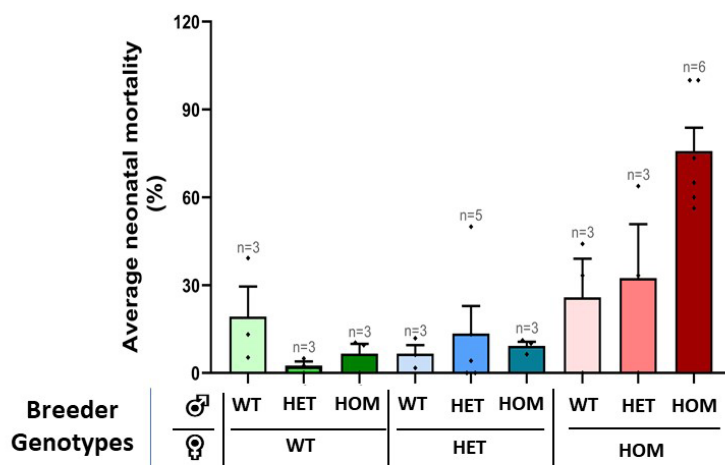
the absence of Mrp4 protein in all KO rat tissues and drug transport studies in tissues and cells of Mrp4 KO rats demonstrated that Mrp4 KO rats had lost Mrp4 transport function. Intriguingly, ~29% of Mrp4 homozygous KO female breeders exhibited substantial frank vaginal bleeding during parturition that required maternal euthanasia. In addition, maternal Mrp4 deficiency promoted neonatal demise - pups born from Mrp4<sup>-/-</sup> breeders had a 75.79% average neonatal mortality rate. Interbreeding of Mrp4 rats of different genotypes demonstrated that the maternal Mrp4 genotype was an essential contributor to the demise of mothers and pups, with a gene-dose effect of the paternal Mrp4 genotype contributing to neonatal mortality. Pathological analysis of two euthanized dams revealed hemorrhage in several organs with a pattern suggestive of severe thrombocytopenia or thrombopathia, accompanied by an altered coagulation profile, supporting the hypothesis of a platelet disorder in the Mrp4 KO rats, resulting in a disease that may be comparable to Glanzmann thrombasthenia. In conclusion, we successfully developed and characterized a Mrp4 KO rat, a model that can be used for preclinical investigations of the pharmacokinetic role of Mrp4 in drug disposition and as a novel model to further probe the platelet disorder with histologic findings similar to those seen in other platelet pathologies such as Glanzmann thrombasthenia.

**Mrp4 KO rat breeder dams exhibit excessive bleeding during/after parturition leading to euthanasia/death**

	WT	HET	KO
Total # of breeder dams	9	11	17
# of breeder dams euthanized/died during/after parturition	0	0	5
% of breeder dams euthanized/died during/after parturition	0%	0%	29.41%

**Table.** Total number and percentage of WT, Mrp4 HET and Mrp4 KO breeder dams that were euthanized/died during/after parturition due to excessive bleeding.

**Maternal Mrp4 deficiency promotes Neonatal demise**



**Figure.** Percentage of neonatal mortality in litters generated from breeding Mrp4 WT, HET and KO male and female rats. "n" on top of each bar represents number of breeding pairs with at least 2 litters.

# JOHN D. SCHUETZ, PHD MEMBER



Investigations in John Schuetz Lab determine how transporters and metabolic pathways impact disease, especially cancer. They have focused on ABC transporters because over a third of the 48 members in this gene family contribute to disease processes. Recent studies reveal how transporter expression affects the underlying biology of acute myeloid leukemia and medulloblastoma. These findings reveal potential targetable liabilities that can, through mechanistic studies, be leveraged to develop novel therapeutic approaches. Thus, these studies provide the basis for targeting transporters and metabolic targets in pre-clinical models of acute myeloid leukemia and medulloblastoma to improve therapeutic response.

Medulloblastoma (MB), a malignant pediatric brain tumor of the cerebellum, is a leading cause of non-accidental death in children and adults, especially children less than 5 yrs. MB is a heterogeneous tumor comprised of four major subgroups: mutations in the WNT and Sonic hedgehog (SHH) developmental pathways; Group3, characterized by MYC overexpression, and the heterogeneous Group 4. Sonic hedgehog (SHH) driven medulloblastoma (MB) acquires resistance to current therapies targeted against smoothened (a key SHH pathway regulator) effecting a poor clinical outcome. We discovered, through bioinformatics and in a murine model of medulloblastoma that ABCC4 was a driver of SHH-MB which likely accounts for why ABCC4 overexpression predicts poor overall survival in SHH-MB. Because suppression of ABCC4 impairs SHH pathway activation, we hypothesized that ABCC4 interacting proteins might also regulate the SHH pathway and identified a new regulator. This knowledge could be applied to a murine SHH-MB model. In total, these findings form the experimental foundation for a new therapeutic approach: target ABCC4 inhibition, which by acting downstream from smoothened (where most of the SHH-MB driver mutations or amplifications occur), should provide an opportunity to improve survival of SHH-MB.

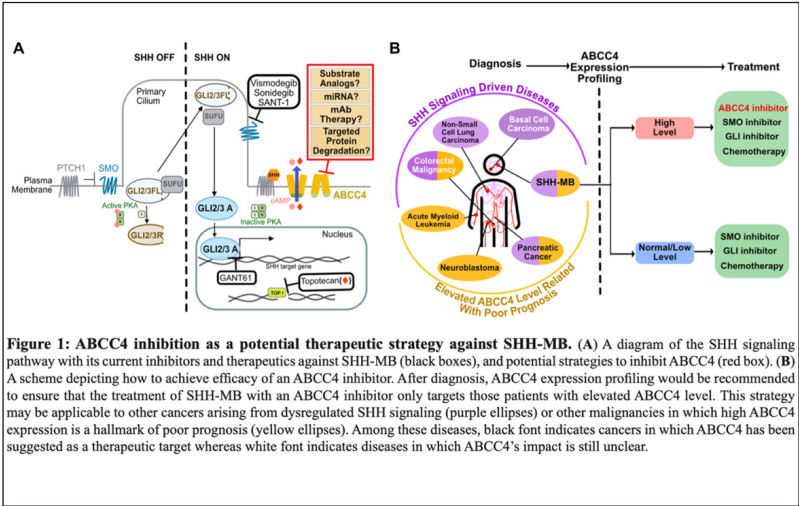
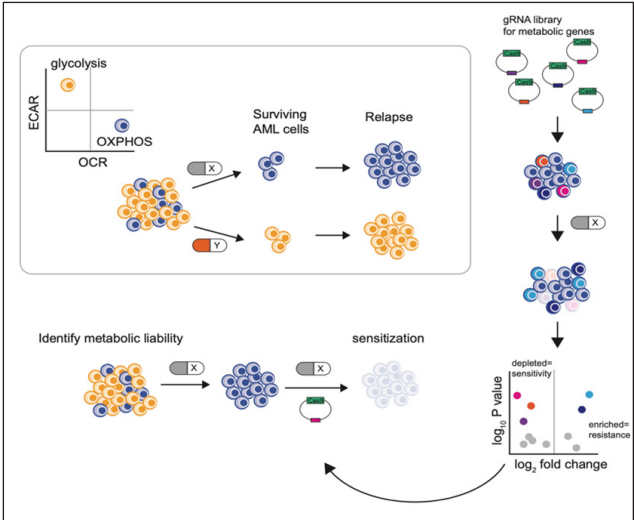


Figure. Reproduced from Oncotarget 2022

Metabolic programs (e.g., glycolysis or oxidative-phosphorylation) vary among subtypes of AML as well as in their leukemic stem cells. The main metabolic programs in AML might impair the efficacy of some chemotherapeutic agents thereby evading thereby and facilitating relapse. Determining if and how chemotherapeutic drugs are impacted by an AML’s metabolic program using a CRISPR metabolic library screen can then be leveraged to identify drug combinations that can be developed to enhance AML therapy.



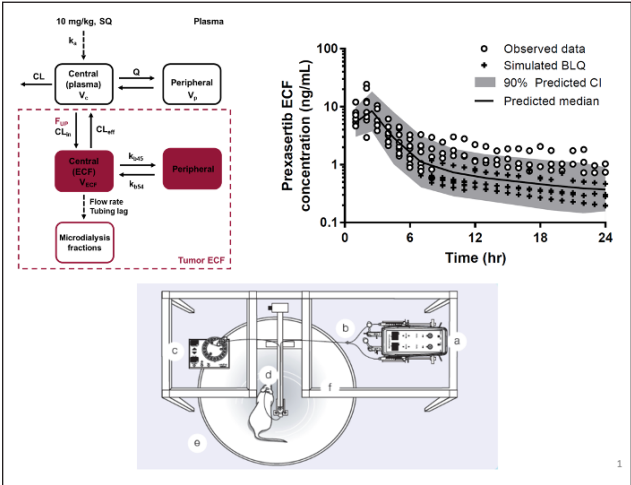
**Figure.** Using CRISPR to identify exploitable metabolic liabilities in AML. AML have a range of metabolic phenotypes assessed by Seahorse showing glycolysis (ECAR, extracellular acidification rate) And Oxidative phosphorylation (OCR, oxygen consumption rate). These Metabolic phenotypes can impact response to chemotherapeutic drugs. A CRISPR screen can uncover which genes and pathways might be exploited to prevent relapse.

# CLINTON F. STEWART, PHARMD MEMBER

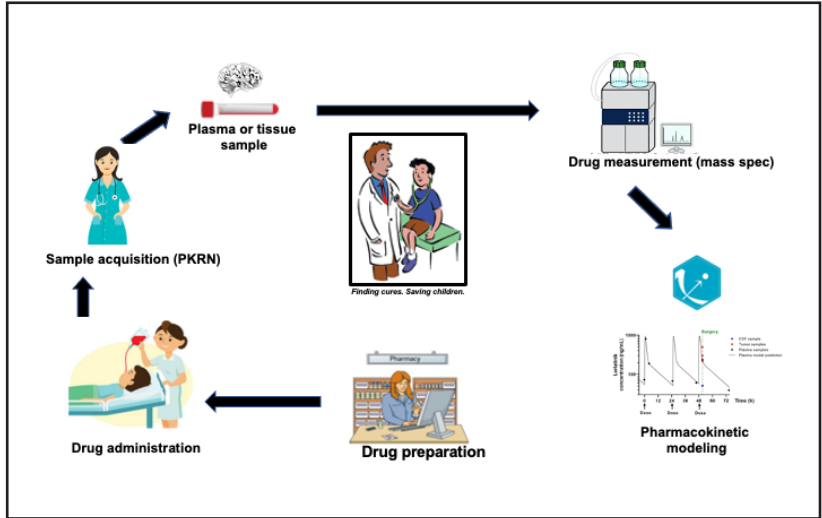


Since joining the Department in 1991, Dr. Stewart's work in the laboratory has focused on translational research of anticancer drugs in children with solid and brain tumors. The Stewart Lab has addressed clinically relevant problems encountered in the therapy of children with brain tumors, primarily the CNS penetration of novel compounds used to treat pediatric brain tumors. The process used includes tumor subgroup-specific models of pediatric CNS tumors grown in mice, cerebral microdialysis sampling of tumor extracellular fluid (tECF) and ventricular CSF, drug measurement using mass spectrometry, and pharmacokinetic modeling and simulation of the derived data to directly assess the unbound partition

coefficient ( $K_{p,uu}$ ) for the drug under study. Results of recent microdialysis studies have been directly translated into the design of clinical trials, for example gemcitabine (Morfouace, *Cancer Cell*, 2014 – SJMB12; NCT01878617), ribociclib (Patel, *Cancer Chemother Pharmacol*, 2019 – SJDAWN; NCT03434262), and prexasertib (Campagne, *Europ J Pharm Sci*, 2020 – NCT04023669).



**Figure.** Using a multi-compartmental pharmacokinetic model, prexasertib concentration-time data were fit. Depicted at the bottom of the figure is a microdialysis set-up

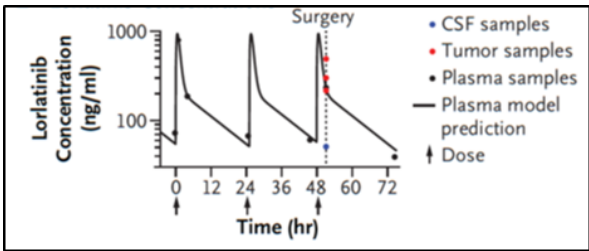


**Figure.** An example of how the Stewart Lab collaborates with clinical investigators to conduct comprehensive clinical pharmacology studies.

patient. For example, the study the disposition of lorlatinib in a 3-year-old child with infantile hemispheric glioma and a SPECC1L– ALK fusion. This patient was begun on the CNS penetrant ALK inhibitor lorlatinib and after improvement in neurologic function and shrinkage in tumor volume, the patient underwent exploratory surgery to remove residual tumor. Pharmacokinetic studies were performed to characterize lorlatinib disposition in plasma, cerebrospinal fluid, and brain tumor tissue obtained at surgery (Bagchi, *New Eng J Med* 2021). Lorlatinib plasma concentration-time data were fitted with a linear two-compartment model, and plasma  $CL/F$  and steady-state  $AUC_{0-24h}$  were 15.5 L/h, and 4044 h·ng/mL, respectively. Lorlatinib tumor tissue to total plasma concentration ratio was  $1.44 \pm 0.6$ . These data support that lorlatinib was CNS penetrant in this patient as in adults and was highly effective to manage this ALK-fused glioma tumor.

As little is known about the disposition of most anti-cancer agents in children with cancer, the Stewart Lab has collaborated with clinical investigators to conduct comprehensive pharmacology studies in clinical trials. These studies include pharmacokinetic, pharmacogenetic, and pharmacodynamic studies to gain a better understanding of the variability in drug disposition in children with cancer. A flow chart of a pharmacokinetic study in presented in the figure to the right and is exemplified by crizotinib (Gibson, *Cancer Chemotherap Pharmacol*, 2021 – SJHG12), ribociclib and everolimus (Lazow, *Neuro-Onc Advances*, 2022 – LEERAD), and crenolanib (Bisbee, *Cancer Chemotherap Pharmacol*, 2022 – SJPDGF).

While most often the Stewart Lab conducts population pharmacokinetic studies as described above, much can be learned about the disposition of a drug from well-designed pharmacokinetic studies of multiple matrices in a single



**Figure.** A concentration-time plot for a 3-year-old child treated with oral lorlatinib 95 mg/m<sup>2</sup>. Sparse plasma samples were obtained, and CSF and tumor samples were obtained during a neurosurgical process with all data fit to a two-compartment pharmacokinetic model.



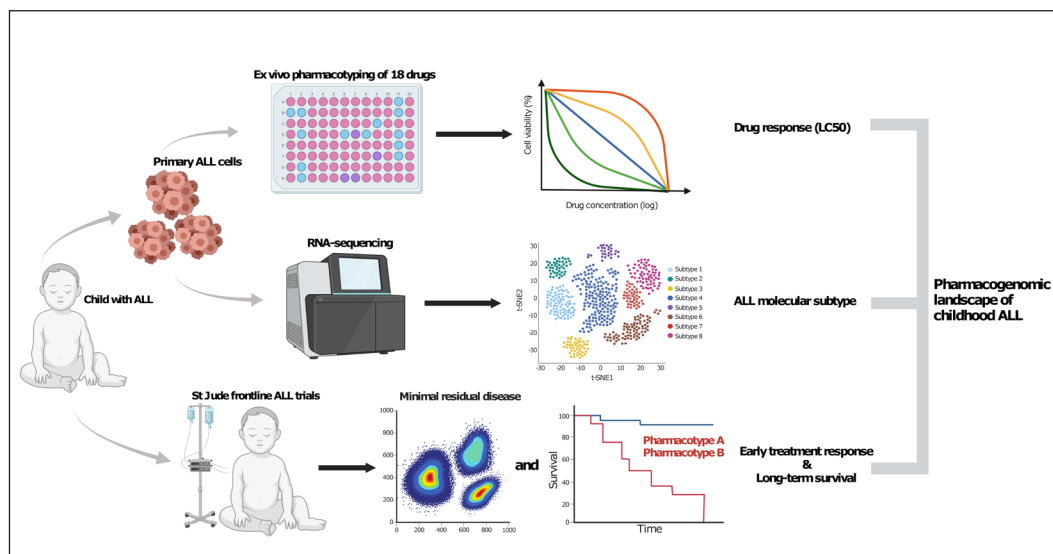
# JUN J. YANG, PHD MEMBER & VICE-CHAIR DIVISION OF PHARMACEUTICAL SCIENCES, ENDOWED CHAIR IN PHARMACOGENOMICS



Dr. Jun J. Yang joined the St. Jude faculty in 2010 and is currently a Member and Endowed Chair in Pharmacogenomics. He also serves as the Vice Chair of the Division of Pharmaceutical Sciences within the department. The Yang Lab studies pharmacogenomics of anti-cancer drugs in children, with a particular focus on childhood acute lymphoblastic leukemia (ALL). Leveraging a wide range of genomics approaches, their research is aimed to elucidate biological factors and processes governing efficacy and toxicity of anticancer drugs, and to then develop pharmacogenomics-guided treatment individualization for children with these catastrophic diseases.

Because genetic factors in both host and tumor genome can affect drug response, the Yang Lab examines inherited (germline) and acquired (somatic) genetic factors for their association with treatment response in childhood ALL. Over the years, we have led a series of genomics studies to identify germline genetic variations associated with minimal residual disease and relapse in racially and ethnically diverse populations (*JAMA* 2009, *Nat Genet* 2011 and 2013, *Lancet Oncol* 2015, *Nat Commun* 2015 and 2019, *Nat Genet* 2022, *JAMA Oncol* 2022).

Focusing on the genomics of drug toxicity, the Yang Lab has developed a highly productive research program related to pharmacogenetics of nucleoside analog drugs. They discovered NUDT15 polymorphism as a major genetic cause of thiopurine toxicity (*J Clin Oncol* 2015), identified biological mechanism by which NUDT15 regulates thiopurine drug metabolism (*Nat Genet* 2016), and exhaustively mapped pharmacogenetic variants in the NUDT15 using high throughput functional genomics techniques (*PNAS* 2020). Based on these discoveries, NUDT15 genetic testing is now included by the US FDA on thiopurine drug label and implemented clinically in US and internationally (*Clin Pharm Thera* 2019). This work has now also extended to antiviral drugs



More recently, the Yang Lab has established a pharmacotyping platform to directly profile patient leukemia cell drug sensitivity using high-content imaging (*Nat Med* 2023). Coupling this with systems pharmacology analyses, they identified novel mechanisms for ALL response to a range of targeted therapeutics and immunotherapeutics (*Nat Cancer* 2021, *Nat Commun* 2022, *Sci Adv* 2022) and are now working on a number of clinical trials to test these agents in children and adults with leukemia.

**Figure.** To comprehensively characterize the relationship between drug sensitivity profiles and in vivo treatment response, we performed ex vivo pharmacotyping of 18 drugs on primary ALL cells from 805 patients treated on the St. Jude Total Therapy XV, XVI and XVII trials. Drug profiling was performed via MTT assay or MSC co-culture with flow cytometry, where we evaluated the LC50 of each drug (dose required to kill 50% of leukemia cells). We also performed RNA-seq for each patient to determine the molecular subtype. Additionally, as part of each therapeutic trial, every patient had mid-induction (day 15) or post-induction (day 42) MRD determined as a measure of in vivo treatment response to chemotherapy. We then performed integrated analyses of drug sensitivities, somatic genomics, MRD and long-term survival outcomes to characterize the pharmacogenomic landscape of childhood ALL. This figure was created using BioRender.com.

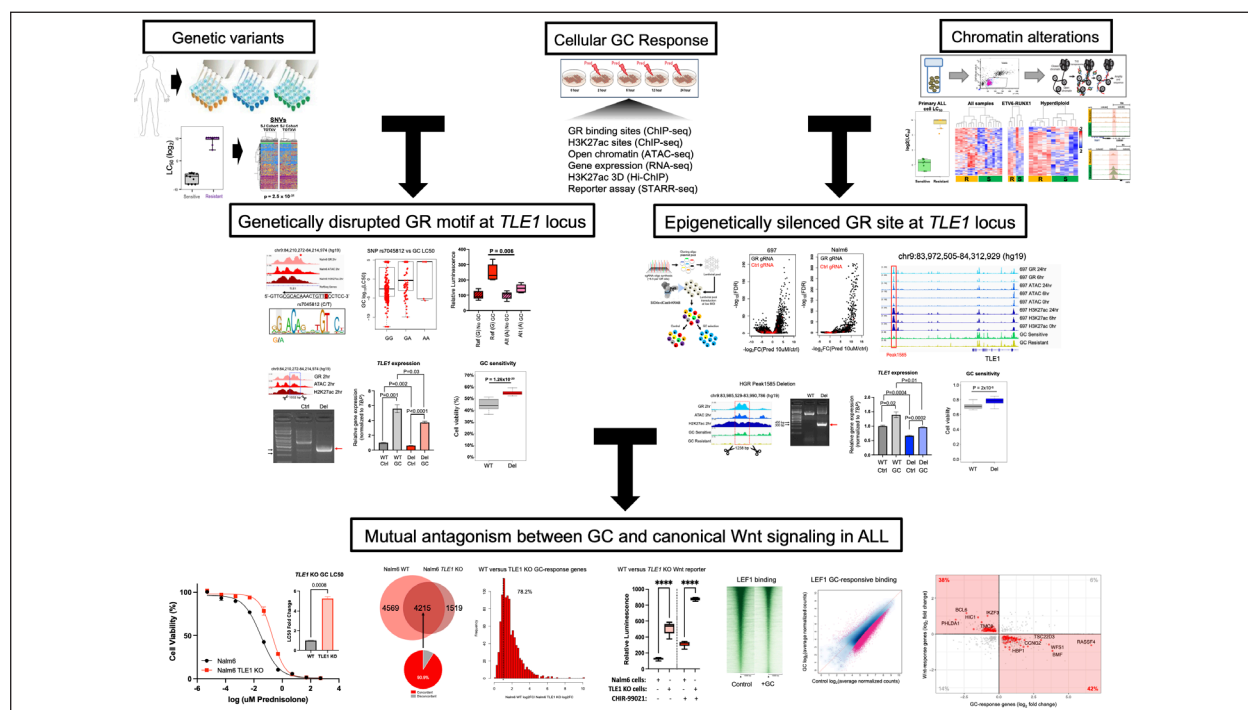
Reference: Lee, S. H., Yang, W., Gocho, Y., John, A., Rowland, L., Smart, B., ... & Yang, J. J. (2023). Pharmacotypes across the genomic landscape of pediatric acute lymphoblastic leukemia and impact on treatment response. *Nature Medicine*, 1-10. <https://doi.org/10.1038/s41591-022-02112-7>

# DANIEL SAVIC, PHD ASSISTANT MEMBER



Dr. Daniel Savic joined the Department of Pharmacy and Pharmaceutical Sciences at St. Jude Children's Research Hospital as an Assistant Member in 2016. He is also a member of the Hematological Malignancies Program at St. Jude and the Pharmacogenomics Research Network (PGRN). His primary research focus involves studying gene regulation in order to identify and functionally characterize cis-regulatory disruptions impacting chemotherapeutic drug response and treatment outcome in childhood acute lymphoblastic leukemia (ALL). For this research, the Savic laboratory utilizes diverse functional genomic and related high-throughput screening approaches (Savic *et al. Genome Research* 2015, Savic *et al. Genome Medicine* 2016, Ramaker and Savic *et al. Genome Research* 2017, Partridge *et al. Nature* 2020).

The Savic research group is working on three areas of research: (i) evaluating cis-regulatory element function and gene regulation in ALL (Diedrich *et al. Leukemia* 2022, Barnett *et al. bioRxiv* 2023), (ii) functionally characterizing inherited noncoding genetic variation that impacts treatment response and relapse in patients with ALL (Bhattarai *et al. medRxiv* 2023) and (iii) mapping gene regulatory responses to chemotherapeutic drugs that impact drug resistance (Ferguson *et al. Blood Advances* 2022, Bergeron *et al. Leukemia* 2022, Bergeron *et al. bioRxiv* 2023). The long-term goal of Dr. Savic's research effort is to improve precision medicine in childhood ALL by gaining a better understanding of genome function and the underlying gene regulatory factors contributing to chemotherapeutic failure in patients.



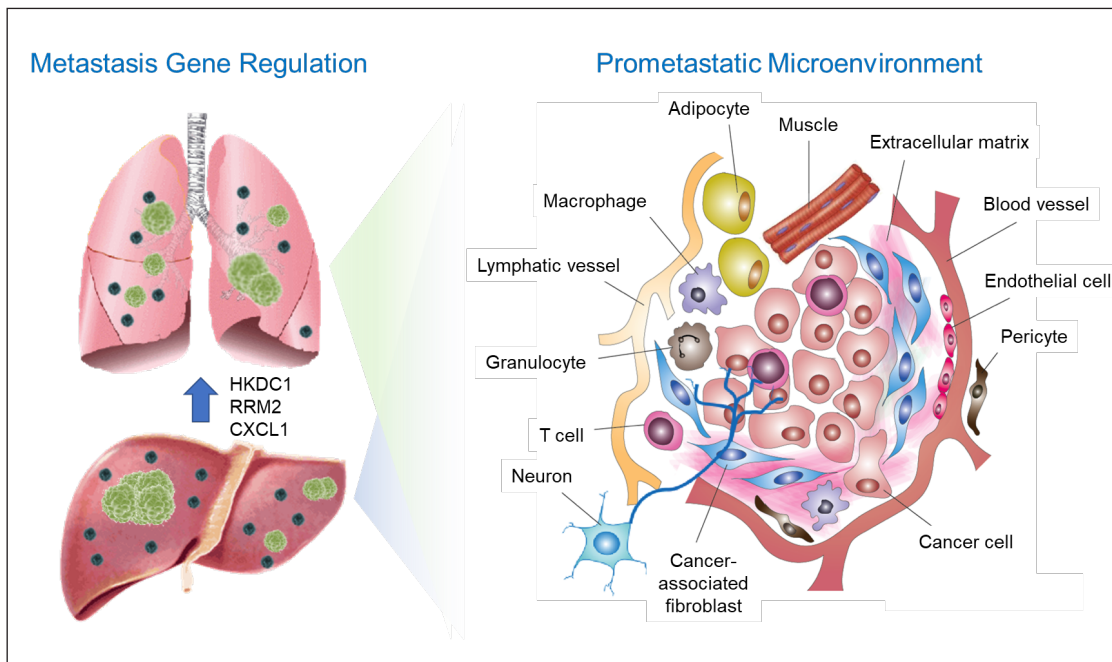
**Figure.** Cis-regulatory disruptions impacting canonical Wnt signaling promote glucocorticoid resistance in childhood acute lymphoblastic leukemia. The GC gene regulatory network was mapped in human ALL cell lines using diverse functional assays (ChIP-seq, ATAC-seq, RNA-seq, HiChIP and STARR-seq). The GC gene regulatory network was further integrated with inherited DNA sequence variants and differentially accessible chromatin sites associated with GC resistance in primary ALL cells from patients enrolled on St. Jude clinical trials. This analysis identified GR-bound cis-regulatory elements at the canonical Wnt signaling repressor TLE1 gene locus that were disrupted in GC-resistant patient samples. Functional evaluation of these GR binding sites using CRISPR genome or CRISPR interference epigenome editing validated their impact on TLE1 gene expression and GC resistance. To better understand the mechanistic relationship between GC signaling and canonical Wnt signaling, we performed additional functional studies that identified extensive crosstalk and mutual antagonism between these two signaling pathways in ALL cells. We determined that antagonism was driven by the binding of GR and the canonical Wnt signaling TF LEF1 to overlapping sets of cis-regulatory elements associated with genes impacting cell death and cell proliferation, and was further accompanied by overlapping and opposing transcriptional programs. Collectively, this study identified cis-regulatory disruptions of canonical Wnt signaling as a novel mechanism impacting GC resistance in childhood ALL and suggest that therapeutic inhibition of canonical Wnt signaling could improve GC sensitivity in patients with resistant disease.

# LIQIN ZHU, PHD ASSISTANT MEMBER



Dr. Liqin Zhu joined the Department of Pharmaceutical Sciences as a Research Associate in 2016 and has been an Assistant Member since 2017. Dr. Zhu previously studied tissue stem cells in global cancer initiation (Zhu *et al. Nature* 2009; Man *et al. Cell* 2015; Zhu *et al. Cell* 2016; Rahrmann *et al. Nature Genetics* 2022). Her current research program focuses on the molecular and cellular mechanisms driving the metastasis and relapse of pediatric and adult liver cancer: (1) elucidate the function of candidate liver cancer metastasis-promoting genes using 3D spheroid models and orthotopic transplantation mouse models; and (2) determine the role of tumor microenvironment in liver cancer metastasis, particularly the spatiotemporal dynamics of tumor-myofibroblast interaction in early tumor mass establishment and late tumor invasion and dissemination; and (3) investigate the newly acquired vulnerability of liver tumor cells induced by standard treatment to identify new drug targets for adjuvant therapies. Using multiple metastatic models of pediatric and adult liver cancer established in their laboratory (Li *et al. Am J Pathol* 2018), the Zhu group has found that: (1) there is a developmentally prometastatic niche to pediatric hepatoblastoma in the neonatal liver mediated by the Cxcl1/Cxcr2 axis (Fan *et al. Hepatology* 2022); (2) tumor-myofibroblast interaction is beyond simple pro- or anti-tumorigenic. Liver cancer metastasis is an ongoing competitive process

between the attempt of myofibroblast to block local growth of the tumor and that of tumor cells to break through the suppression in a Vcam1-dependent manner (manuscript under revision); and (3) there is a dynamic, reversible switching between the two ribonucleotide reductase M2 subunits, RRM2 and RRM2B, that supports the transition of hepatoblastoma cells between a growing state and a surviving state under standard chemotherapy (manuscript under revision). Through these studies, it has become evident that the molecular and cellular networks supporting liver tumor metastasis and drug response are highly plastic and dependent on changes in both intra- and extra-tumoral microenvironment. Secreted proteins mediating tumor-microenvironment interaction are likely potent regulators of liver tumor cell survival, dissemination, and drug response, which provides an exciting scientific rationale for targeting tumor secretome as a new therapeutic strategy for liver cancer. Work in the Zhu lab is supported by American Cancer Society and NIH/NCI.



**Figure.** Gene regulation and tumor microenvironment in liver cancer metastasis

# The Pharmacokinetics Shared Resource (PKSR)

The Pharmacokinetics Shared Resource (PKSR) is part of the NCI-designated St. Jude Comprehensive Cancer Center and is housed within the Division of Pharmaceutical Sciences laboratory space. The PKSR aims to facilitate high-quality, competitively funded, peer-reviewed pharmacokinetic (PK) and pharmacodynamic (PD) research by St. Jude clinical investigators. Through centralized research infrastructure, the PKSR supports investigators in designing, implementing, and conducting the highest-quality PK/PD in Phase I-III clinical trials.



**Mark Leggas, PhD**  
Director



**Kristine Crews, PharmD**  
Associate Director

Dr. Mark Leggas directs the PKSR, and Dr. Kristine Crews is the Associate Director. Together, they supervise a staff of technologists, a biomedical modeler, a coordinator, and research nurses, all fully integrated into the clinical research and pharmaceutical sciences enterprise to ensure that all clinical PK/PD research is consistently supported. In the past year, the PKSR was used by 141 investigators across clinical disciplines.

In the upcoming year, the PKSR will finalize a 5-year strategic plan with the assistance of the Strategic Planning and Decision Support Office at St. Jude. The 5-year strategic plan will confirm that the goals and actions of the PKSR are aligned with those of the Comprehensive Cancer Center and the institution and will create a framework for future direction, operational decision-making, and resource investment of the shared resource.

The PKSR supports PKPD research through these four functions:

1. Assist investigators with the 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 development, implementation, validation, and ongoing quality control. Analytical assay development and implementation include 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. Carl Panetta and the department faculty assist with biomedical modeling, which has three main phases: model design, sampling strategies, and data analysis. The modeling results are used to better understand clinical outcomes and facilitate the design of future trials.



# The Clinical Pharmacokinetics (CPK) Laboratory

The Clinical Pharmacokinetics (CPK) Laboratory, located in the Division of Pharmaceutical Sciences, 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 CPK lab is certified as a high complexity laboratory by CLIA (Clinical Laboratory Improvement Amendments) 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 9000 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  $^{99m}\text{Tc}$ - DTPA. Some of our resources include random access immunochemistry analyzers (e.g. Abbott Architect) and analytical instrumentation (e.g. LC-MS/MS, HPLC).



**Alejandro Molinelli, PhD**  
Director, Pharmacokinetics Lab

Most of our instruments have bidirectional interfaces with the Epic electronic health record. 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 drug effects. 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 to bring cutting edge care to our patients.

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 St. Jude clinical trials, for the Pharmacokinetics Shared Resource.



# The Pharmacotyping Resource

The Pharmacotyping Resource, located within the Division of Pharmaceutical Sciences, supports the St. Jude value of “Embrace the challenge to create a new tomorrow.” The resource has developed a state-of-the-art imaging platform to test drug sensitivity profiles (pharmacotyping) of primary patient tumor cells as a functional precision medicine method. Directed by Drs. Jun Yang and Kristine Crews, this resource is supported by a team of research technologists with expertise in high-content imaging, deep machine learning, drug assay development, preclinical drug evaluation, and research informatics.



**Jun J. Yang, PhD**  
Director



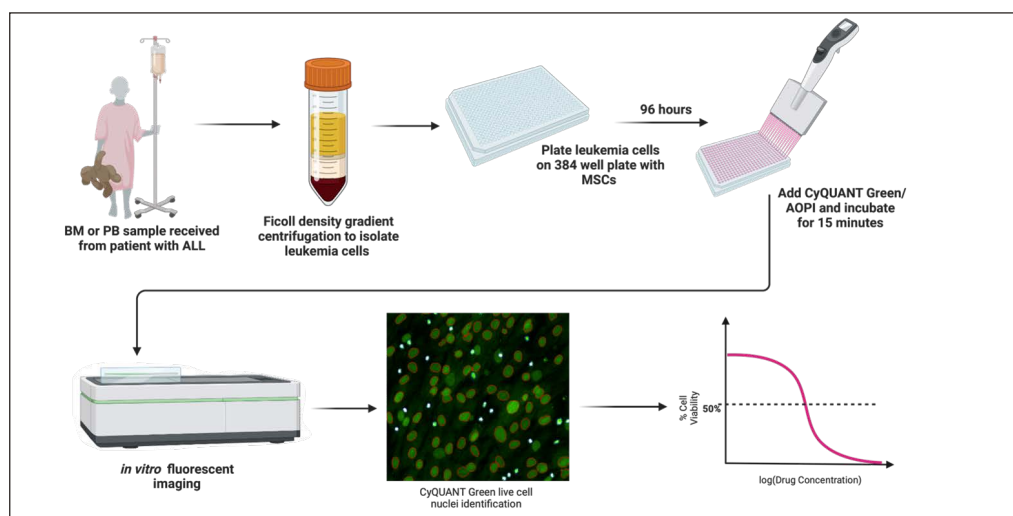
**Kristine Crews, PharmD**  
Associate Director

Over the past 40 years, pharmacogenomics has been a central research endeavor of the Pharmaceutical Sciences Department at St. Jude. Our discoveries of the genetic determinants of drug toxicity and response have fundamentally improved pediatric cancer therapy and made St. Jude a leader in pharmacogenomics-driven precision medicine. Pharmacotyping, i.e., defining inter-patient variability in drug sensitivity, is the essential starting point for correlating drug sensitivity phenotype to patient genomic profiles. Building upon our historical strength in this field, we use a modern pharmacotyping platform to have the potential to drive research to discover new subtype-specific therapeutic opportunities for leukemia.

To this end, the Pharmacotyping Resource is equipped with a PerkinElmer Operetta CLS high-content analysis system for imaging-based drug sensitivity testing. The Operetta CLS is an automated confocal spinning disk fluorescence microscope. It is capable of imaging in 96 or 384 well plate formats. This imager is combined with the PerkinElmer Harmony data analysis software that allows for quantitative image analysis with machine learning image analysis capabilities.

The team has validated the pharmacotyping assay in tumor cells collected from leukemia patients treated on clinical trials of the Hematological Malignancies Program. Leukemia cells obtained from patients are tested for ex vivo sensitivity to 40 anti-leukemia drugs, and genomic profiling is done in parallel by whole genome sequencing and other assays. Our recently published data showed wide variability among patients in drug sensitivity, and an association between sensitivity profiles and event free survival. These findings point to therapeutic implications of genomic alterations in ALL. The integration of tumor cell sensitivity measures with genomic data will drive forward pharmacogenomics discovery research at St. Jude and will guide the development of the next generation of pediatric cancer therapy at St. Jude and beyond.

The mission of the Pharmacotyping Resource is to leverage new drug screening technology to enable collaborative pharmacogenomics research that will translate into improved cancer treatment outcomes in the future.



**Figure.** Overview of the pharmacotyping process. Leukemia cells are collected from patients and drug sensitivity is evaluated using a fluorescence imaging-based assay to characterize the sensitivity to 40 anti-leukemia agents.

# Pharmacogenomics Research & Implementation

Pharmacogenomics research & implementation is a particular strength of the Department of Pharmacy and Pharmaceutical Sciences. Through the department's Clinical Pharmacogenomics Program, pharmacogenomic testing continues to be implemented to benefit St. Jude patients, and actively disseminates resources to advance pharmacogenomics implementation for patients worldwide. The Clinical Pharmacogenomics program aims to fully integrate preemptive pharmacogenomic testing into patient care to improve the safety and efficacy of medication use. Our efforts are informed by a rich history of clinical pharmacogenomics led by our Department, including clinical pharmacogenomic testing for TPMT (thiopurine methyltransferase) deficiency to guide thiopurine use at St. Jude since the 1990s. The multidisciplinary PG4KDS protocol was opened in 2011 (PI: Dr. Cyrine Haidar), with a goal to implement pre-emptive pharmacogenomic testing for all actively treated patients at St. Jude.

In preparation for this undertaking and to facilitate evidencebased clinical pharmacogenomic testing worldwide, Dr. Mary Relling co-created the Clinical Pharmacogenetics Implementation Consortium (CPIC®) [www.cpicpgx.org](http://www.cpicpgx.org) with Dr. Teri Klein of Stanford (U01 GM61393, R24 GM115264, U24 HG 010135). St. Jude is heavily involved with CPIC, with Dr. Kelly Caudle as co-PI and Director of CPIC, Dr. James Hoffman as co-leader of CPIC informatics, and with much involvement from Dr. Cyrine Haidar (SJ Clinical Pharmacogenomics Senior Program Manager), Dr. Kristine Crews (Director, PGY2 Residency in Clinical Pharmacogenomics), Dr. Alejandro Molinelli (Director, PK Clinical Lab), and others. CPIC has published 26 clinical practice guidelines covering 25 genes and over 100 drugs with many updated at least once and has become widely recognized as providing a gold standard resource for clinical implementation of pharmacogenomics. CPIC is endorsed by leading pharmacy (ASHP) and clinical pharmacology organizations

(ASCPT), has been recognized by the College of American Pathologists (CAP), and is now incorporated as part of ClinGen <https://clinicalgenome.org/> as an authoritative resource for pharmacogenomic curation. There is direct intersection between CPIC and the Clinical Pharmacogenomics Program, as the eventual goal at St. Jude is to implement all genes and drugs encompassed by CPIC guidelines. As of 2022, the Clinical Pharmacogenomics Program has implemented 14 genes and 66 drugs at St. Jude through the PG4KDS protocol. Over 7,000 patients have consented for pre-emptive pharmacogenomic testing. The implementation of clinical pharmacogenomics is conducted in close collaboration with Information Services and the clinical departments to create clinical decision support alerts to guide rational prescribing (both pre-test and post-test alerts). Publications, presentations, and resources are made freely available via the PG4KDS website ([www.stjude.org/pg4kds](http://www.stjude.org/pg4kds)). A multidisciplinary Pharmacogenomics Oversight Committee provides oversight. As each gene/drug pair is implemented, the results are placed in the electronic health care records of all past (and future) patients. All tests are handled through the PK Clinical Lab, and are accompanied by consults entered by a clinical pharmacist. Examples of common highrisk drugs whose prescribing is improved include ondansetron, proton pump inhibitors, voriconazole, thiopurines, opioids, antidepressants, and inhaled fluorinated anesthetics. Some interventions, such as the goal to genotype 100% of leukemia patients for TPMT and NUDT15 prior to first dose of thiopurines, are tracked as institutional medication safety metrics.

The Clinical Pharmacogenomics Program personnel are committed to train the next generation of pharmacogenomics professionals through the PGY2 residency in Clinical Pharmacogenomics and to educate health care professionals and patients. At the same time, CPIC membership has grown to over 500 members of international clinicians and scientists and continues to provide education and valuable resources to facilitate the implementation of pharmacogenomics into clinical practice worldwide.



Kelly Caudle, PharmD, PhD



Kristine Crews, PharmD



Cyrine Haidar, PharmD



James Hoffman, PharmD, MS



Nancy Kornegay, MBA



Mary Relling, PharmD



# Pharmaceutical Services

is led by Dr. William Greene and is staffed by pharmacists, pharmacy technicians, research and administrative staff, and faculty, (see Organizational Chart, page 6) all dedicated to addressing patient care needs as we focus on providing the best pharmaceutical care required for each child at St. Jude while supporting a collective research endeavor. Our personnel, working with other clinicians in a cutting-edge, highly collaborative environment, assure the best possible outcomes of drug therapy. Nearly 150 pharmacy staff are involved in these care efforts. Their work is simultaneously focused on integrating optimal conduct of St. Jude's medication-related clinical research, helping to fulfill our organizational mission to "advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment." Twenty-five pharmacists are certified as specialists by the Board of Pharmacy Specialties, and four other pharmacists carry at least one credential from other certifying organizations, testifying to the commitment of staff to deep understanding and high level of clinical practice of pharmacotherapy and research. Current Mission, Vision, and Strategic Priorities for Pharmaceutical Services are defined below.



**William Greene, PharmD**  
Chief Pharmaceutical Officer

## Pharmaceutical Services Strategic Plan FY21-22

### Mission:

Pharmaceutical Services is a part of the larger Department of Pharmacy and Pharmaceutical Sciences and is focused on the patient-care services of the department. Our mission is to provide the highest quality comprehensive pharmaceutical care to children with catastrophic diseases, always working to integrate research findings into clinical care as quickly as possible.

### Vision:

The vision of Pharmaceutical Services is to provide excellent pharmaceutical care, facilitate the generation of new knowledge related to drug therapy, and be recognized on a national level for excellence in patient care, practice-related research, and education of professionals regarding drug therapy for children with catastrophic illnesses.

#### Pharmaceutical Care

Provide the highest quality comprehensive pharmaceutical care to children with catastrophic diseases

#### Professional Growth and Teamwork

Cultivate an environment that facilitates and encourages professional growth and teamwork

#### Shared Knowledge

Share knowledge and improvements through data, publications and presentations.

#### Compliance/Regulatory

Ensure ongoing compliance with all applicable laws and regulations.

#### Medication Use Systems, Data and Technology

Improve and assure optimal design and functioning of medication use systems and technology.

**Figure.** Strategic Plan for Pharmaceutical Services

The proactively identified priorities of "Professional Growth and Teamwork" and "Shared Knowledge" help to drive a culture of professional engagement. St. Jude has an ongoing relationship with the University of Tennessee College of Pharmacy and accepts students from other colleges of pharmacy for the purpose of experiential training. Typically, the department supports 60 or more months of student training each year. Four (soon to be five with the addition of a program in Infectious Diseases Pharmacy) PGY2 Pharmacy Residency programs further enhance the culture of learning and growth and help to support academic pursuits and publications. During 2022, staff from Pharmaceutical Services were co-authors on at least 7 publications and provided more than 8 presentations at national/state professional organization meetings; this occurred even while the entire organization was fully immersed in a total conversion/implementation of a new electronic health record.



# Pharmacy Clinical Dispensing Operations

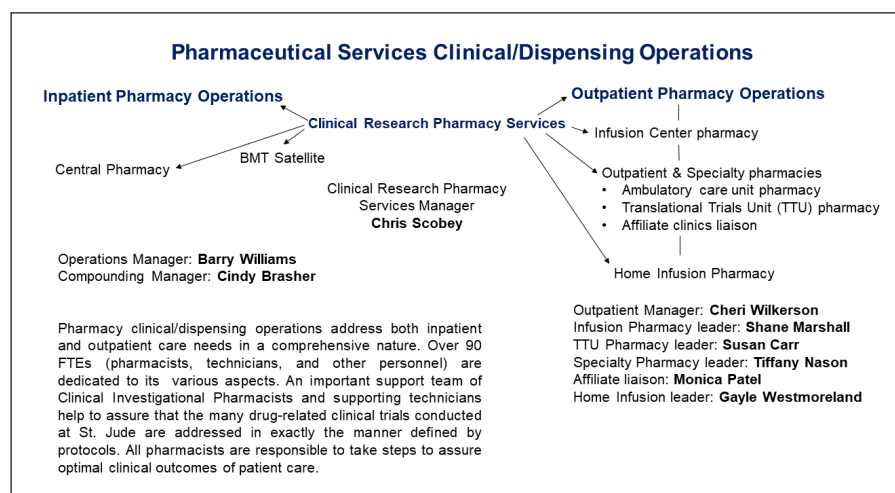
are led by Dr. William Humphrey (Acute Care; also Pharmacist In Charge) and Dr. Steve Pate (Outpatient Care, and current Interim Chief Pharmaceutical Officer). Pharmaceutical Services addresses the needs of St. Jude patients comprehensively across the continuum of care – providing services while they are inpatients, during outpatient clinic visits, and while they are in domiciliary facilities or at home. When patients from outside the Memphis region return home, care continues as pharmacists assure attention to relevant clinical issues as well as continued provision of needed medications. Services provided by Clinical Staff Pharmacists and Certified Pharmacy Technicians focus on assuring optimal inpatient and outpatient care delivery in a manner consistent with the defined research protocol or non-protocol plan of care. While technical staff focus on safe and precise preparation and provision of medications, pharmacists assure that medications (and their doses) ordered for care of these patients are optimally managed and absolutely consistent with the plans of any defined research protocol – preventing unintended consequences of complex therapeutic regimens that may result in either harm or failure to achieve the goal of therapy. These same pharmacists serve as patient and family educators and as resources to our patients and families when drug-related questions arise. Clinical Staff Pharmacists collaborate with Clinical Pharmacy Specialists (see page 6) to assure proper conduct of medication reconciliation as patients move from inpatient to outpatient care and back. A team of Clinical Research Pharmacists and Certified Pharmacy Technicians help to assure the effective and efficient conduct of the many drug-related clinical research trials conducted through St. Jude. This team assures the proper development of protocols, handling of investigational drugs, and development of information for all pharmacy staff related to each protocol. Each pharmacist at St. Jude is dedicated to our research mission and is responsible to assess and assure proper compliance of drug therapy with the definitions of each unique protocol to which the individual patient is consented. Because medications are shipped into many states across the nation, careful attention is devoted to compliance with the unique regulatory requirements of each state. Similarly, the broad geographic dispersion of patients seen at St. Jude requires interaction with a multitude of state-based and commercial insurance programs, requiring attention to the requirements in order to pursue reimbursement of any kind. Specialty Pharmacy services which are dually accredited by URAC and by ACHC are also provided by the Outpatient Care team and help to assure optimal use of these high cost/high-risk medications and facilitate reimbursement by insurers.



**William Humphrey, BS Pharm, MS, MBA**  
Director, Pharmacy Operations



**Steve Pate, BS Pharm**  
Director, Outpatient Pharmacy Services



Clinical Dispensing Operations Services extends beyond the typical inpatient and outpatient pharmacy services as St. Jude provides home infusion therapy to patients who require medications while at home or in a local domicile. This service routinely provides a broad variety of medications to support therapy in the local delivery area and works with outside agencies to assure provision of such therapy to patients when they are located outside the local delivery area. This Home Infusion Service was recognized as exhibiting several “best practices” during its most recent accreditation by The Joint Commission. Finally, the department collaborates directly with our 8 St. Jude Affiliates to help assure that St. Jude patients being managed at these locations throughout the United States have all their medication-related needs addressed.

**Figure.** Clinical Dispensing Operations

# Clinical Pharmacy Services

are led by Dr. John McCormick. Clinical Pharmacy Specialists extend the reach of Pharmaceutical Services directly into the patient care team and to the patient. Specific teams currently addressed by these clinicians include Leukemia/Lymphoma, Solid Tumor, Neuro-Oncology, Bone Marrow Transplant & Cellular Therapy, Chemotherapy, Intensive Care, Surgery, (non-malignant) Hematology, and HIV clinic. These board-certified pharmacists are credentialed members of the medical staff with collaborative authority to perform direct patient assessment and prescribe medication therapy and associated laboratory tests for patients assigned to their teams. As members of the medical staff, Clinical Pharmacy Specialists provide routine clinical pharmacy services in both the inpatient and outpatient setting to ensure optimal prescribing and monitoring of medication therapy for patients assigned to their team. This includes the use of individualized pharmacokinetics and targeted therapy for antineoplastics and other medications, and consideration of clinical pharmacogenomics in defining drug use and dosing approaches. These individuals also work closely with clinicians to provide oversight and development of care plans (non-protocol treatment plan) for patients who are not managed according to an approved research protocol and provide departmental and institutional support for research protocol development and implementation. These pharmacists also offer educational opportunities for colleagues (both internal and external) as well as training for residents and students in pediatric oncology and hematology medication management and disease states. Unique clinical pharmacy programs focus on Antimicrobial Stewardship (2 dedicated FTEs) and Clinical Pharmacogenomics (see page 23). St. Jude is recognized as an "Antimicrobial Stewardship Center of Excellence" by the Infectious Diseases Society of America, reflecting the effective integration of this program into clinical care processes and care teams. This effort is an ongoing collaboration between our department and the Department of Infectious Diseases, and routinely engages team-based Clinical Pharmacy Specialists as well as Infectious Diseases Faculty and Fellows impacting clinical care decisions. In 2023, St. Jude will collaborate with LeBonheur Children's Hospital Department of Pharmacy, with grant support from the Society of Infectious Disease Pharmacists, to initiate a post-graduate year-2 residency experience focused in Infectious Diseases Pharmacy. In addition, members of this team have facilitated development of the Pharmacogenomics Committee within the Children's Oncology Group. Moreover, the efforts and impact of Clinical Pharmacy Services now reach globally with the establishment of a Clinical Pharmacy Specialist position in our Global Pediatric Medicine program. The outstanding contribution of the individuals who provide Clinical Pharmacy services was further recognized with receipt of the Clinical Care Improvement Award for the institution in 2020 and the Weaver-Penna Award from the Board of Pharmaceutical Specialties in 2021.



**John McCormick, PharmD,**  
Director, Clinical Pharmacy  
Programs



**Figure.** Clinical Pharmacy Specialist Services

# The Pharmaceutical Services Medication Safety and Policy Team

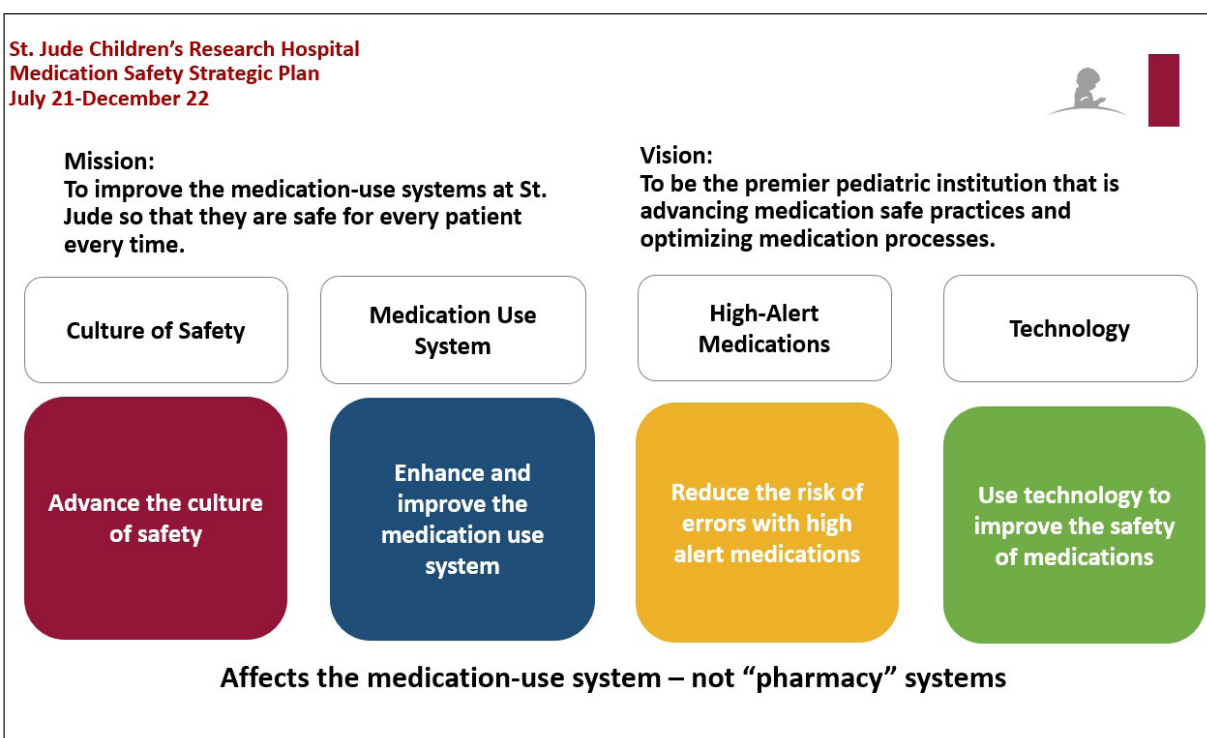
, led by Dr. Jennifer Robertson, is responsible for ensuring safe medication systems throughout St. Jude. Discrete functions include setting and revising of policies related to medication use within the institution, routine and ongoing efforts to improve the safety of medication use systems (based on both reactive and proactive review of events and risk), establishment and maintenance of high-quality drug information resources and drug therapy guidelines, maintenance of drug formulary and implementation of cost savings efforts when relevant, and support of ongoing performance improvement related to medication use. Many refinements of the system are accomplished each year, impacting physicians, advanced practice providers, nurses, and pharmacists as they provide patient care.



**Jennifer Robertson, PharmD**  
Director, Medication Outcomes & Safety

The team works with the institution's Medication Use Safety Team (MUST) to complete actions outlined in the latest Medication Safety Strategic Plan. The plan continues to focus on culture of safety, improvement of medication use systems, high-alert medications, and use of technology to improve the safety of medications. The 2022 plan's major emphasis was to provide leadership and guidance for key medication safety and high-risk medication workflows while implementing a new electronic health record (EHR). In 2023, the Strategic Plan will be updated and include actions to maximize the safety of the new EHR as well as other initiatives.

Significant contributions from Dr. Robertson's team in 2022 included a multimillion-dollar savings from the use of biosimilars for colony stimulating factors and the coordination of a performance improvement project that led to a 30% improvement in compliance with use of pump dose error reduction software (i.e., dosing checks and alerts on the medication pumps).



**Figure.** Medication Safety Strategic Plan

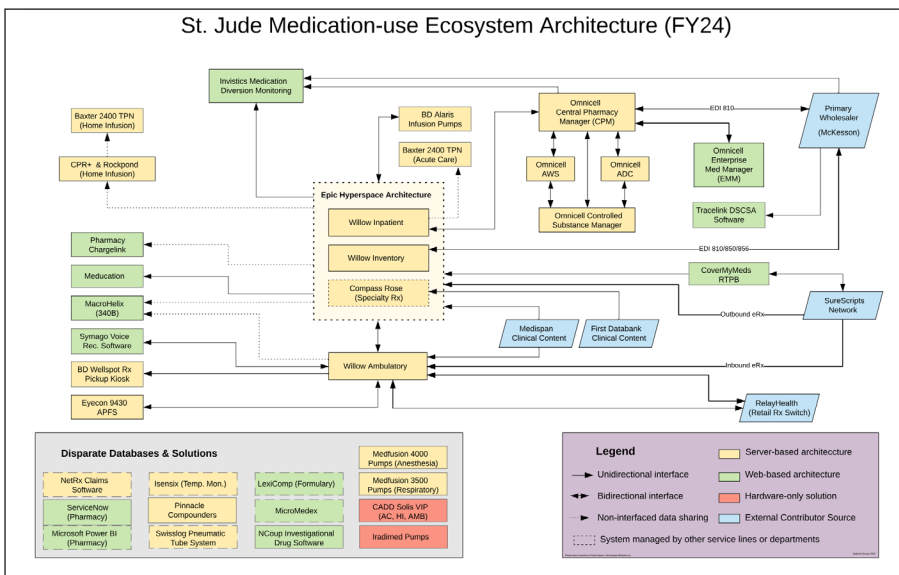
# Pharmacy Informatics,

Led by Dr. David Aguero, the **Pharmacy Informatics** Community aims to implement, maintain, and optimize best-in-class medication use technology solutions and analytics, in support of exceptional pharmaceutical care. Through collaboration with clinical staff (our customers), Quality and Patient Care, and Information Services, Pharmacy Informatics strives to facilitate practical solutions that achieve optimal patient outcomes, workflow efficiency, and resource stewardship within the medication use process at St. Jude Children's Research Hospital. The informatics ecosystem at St. Jude is quite complex and is illustrated below (see Figure 23). The work of this team helps assure that this complex system is both functional and achieves the intended outcome of patient management, resulting in excellent patient care. In addition to this ecosystem, a host of different solutions and their functionality are maintained by this team. These solutions range from inventory control tools to infusion pumps to financial systems and drug information systems and include important trial randomization software.



**David Aguero, PharmD**  
Director, Medication Systems & Informatics

Additionally, Pharmacy Analytics Services maintains a business intelligence portfolio as part of the departmental data strategy. This team assures the access and use of data created during



**Figure.** St. Jude Medication Use Ecosystem

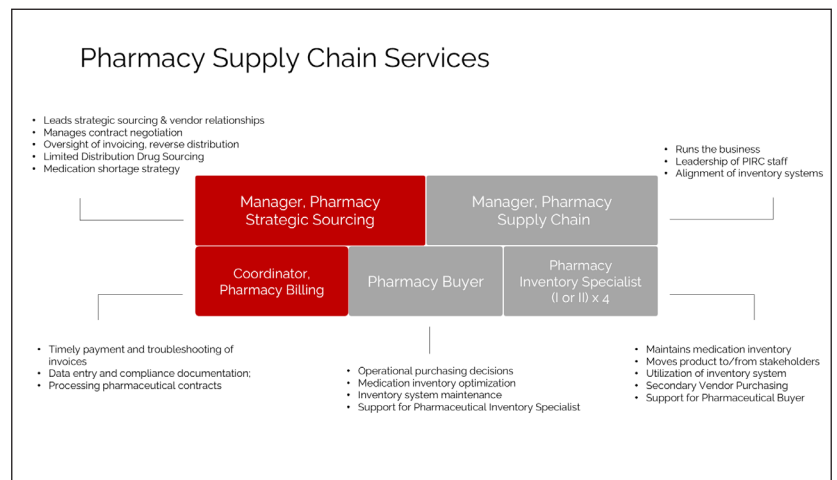
meet department needs, data is migrated to Microsoft Azure and projected through dashboards to support data-driven decisions throughout the organization.

## Pharmacy Supply Chain Services

Dr. Aguero is also responsible for Pharmacy Supply Chain Services and leading an operational coalition of our department leaders who support the team in managing the challenging pharmaceutical supply chain landscape. The service line is focused into two areas (see Figure below):

- Strategic sourcing is responsible for managing pharmaceutical vendor relationships, accounts payable, contracts, and drug shortage monitoring. The group collaborates with our Group Purchasing Organization (Vizient) and leverages our strategic partner with McKesson to reinforce consistent supply while being mindful of St. Jude resources.

- Pharmacy supply chain operations is responsible for managing inventory movement to and from stakeholders, vendor purchasing decisions, inventory optimizations, and alignment of inventory systems and compliance, and ensuring customer service is consistent.





# Our PGY2 Residencies in Oncology Pharmacy, Medication Use Safety and Policy, Clinical Pharmacogenomics and Informatics

are led by Program Directors, Drs. Jennifer Pauley, Jennifer Robertson, Kristine Crews, and David Aguero. All programs are accredited by the American Society of Health System Pharmacists (ASHP; NOTE – Informatics residency considered “candidate” status). Trainees at St. Jude are supported by an institutional Clinical Education and Training Office, 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. Further details are available on the St. Jude website, [www.stjude.org/pharmacyresidency](http://www.stjude.org/pharmacyresidency).

## St. Jude PGY2 Pharmacy Residents, FY23



Madison Cole, PharmD



Chad Compagner, PharmD



Rachael Stone, PharmD



Katelyn Phillips, PharmD

# HONORS & AWARDS

**Cyrine Haidar, PharmD**, has been appointed to the EPIC Genetics Specialty Steering Board.

**James Hoffman, PharmD, MS**, has been promoted to Senior Vice President for Quality and Safety. He also recently received the 2022 ALSAC/St. Jude Partnership Award presented by ALSAC. With this award, Dr. Hoffman is recognized by ALSAC for his efforts throughout the COVID pandemic playing a significant role in ensuring the health and safety of everyone on our campus, including the ALSAC and St. Jude staff, vendors and most importantly our patients and patient families.

**Dave Rogers, PharmD, PhD**, Chair, Department of Pharmacy and Pharmaceutical Sciences, has been elected to a 3-year term as a trustee of the American College of Clinical Pharmacy (ACCP) Foundation.

**Jun Yang, PhD**, Vice Chair for Pharmaceutical Sciences, has been named the St. Jude Endowed Chair in Pharmacogenomics. An endowed chair represents the highest academic honor that St. Jude bestows upon its faculty members. This endowment provides support for the recipients' salary and research programs.

**William Evans, PharmD, Mary Relling, PharmD, and Kelly Caudle, PharmD, PhD**, are three St. Jude scientists and researchers who have been named to the 2020 list of Highly Cited Researchers.

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## St. Jude Values - Department Nominees

Two employees were featured in this year's St. Jude Values Book.

### Delia Carias, PharmD



Whether by easing symptoms and side effects or by providing cures, medications are indisputably important when treating children with devastating diseases. But who makes sure the St. Jude drug arsenal contains the most effective options at the best cost? For that task, Delia Carias, PharmD, willingly stands front and center.

Earlier this year, Carias completed an exhaustive review of the hospital's drug formulary—the thousands of medications clinicians use to help patients—resulting in a savings of

\$2.5 million. She knew she couldn't do this alone, of course. Carias collaborated with many departments and groups on campus to assess how much each drug in the hospital's formulary costs, along with how much of that cost is typically reimbursed by health insurers.

Even more crucial to her calculations was patient safety. Carias took pains to thoroughly tease out what medication changes would mean to patients, ensuring that no children would be inconvenienced or harmed.

Carias wasn't assigned this challenge. She tackled it willingly, envisioning the potential for huge cost savings with low risk. She saw the value her efforts might bring, and her colleagues see the value in her determination to make the most of St. Jude resources.

*Nominated by:*  
*Jennifer Robertson, PharmD*  
*Pharmaceutical Services*

### Alejandro Mollinelli, PhD



When the right drug is given to the right patient at the right dose, the stage is perfectly set for a better outcome. This is the ideal Alejandro Mollinelli, PhD, strives for every day.

As director of the Clinical Pharmacokinetics Laboratory, Mollinelli provides a special skill set in accurately measuring drug concentrations in patient samples allowing our clinical pharmacists to tailor doses to meet every patient's unique needs.

It's an enormous task for the lab, which processes and analyzes about 9,000 clinical samples every year and sends another 300 to other laboratories. Mollinelli and his colleagues work with St. Jude pharmacists to painstakingly review each drug dose clinicians request for every patient. These patients include infants—whose small bodies may only tolerate the tiniest amounts—to teenagers with serious diseases requiring stronger doses. The unique collaboration ensures patients receive the best possible treatment, all while staving off troublesome or debilitating drug side effects that can hamper their ability to play and learn.

His upbeat, cheerful manner belies Mollinelli's role as a secret weapon at St. Jude to save the next child and find the next cure.

*Nominated by:*  
*P. David Rogers, PharmD, PhD*  
*Pharmacy and Pharmaceutical Sciences*

# DEPARTMENTAL EXTRAMURAL FUNDING

## New Awards FY2022

### James Hoffman

AHRQ R18 - \$26,840 - 08/2021 - 07/2022  
Spread of Safety Interventions: Planning for Context

### Mark Leggas

NIH R01 - \$224,166 - 03/2022 - 02/2023  
Non-opiate treatment after prenatal opiate exposure to Prevent Postnatal Injury to the Young Brain (No-POPPY)

### Mark Leggas

NIH R01 - Supplement - \$360,502 - 03/2022 - 02/2023  
Supplement - Non-opiate Treatment After Prenatal Opiate Exposure to Prevent Postnatal Injury to the Young Brain (No-POPPY)

### Mark Leggas

NIH R01 - \$115,810 - 02/2022 - 05/2022  
Mechanistic and Pharmacologic Studies of Selective Mithramycin Analogues Targeting EWS-FLI1 in Ewing Sarcoma

### Jun J. Yang

NCI R43 - \$80,000 - 08/2021 - 07/2022  
Development of companion diagnostics for dasatinib-based personalized therapy for T-ALL

### Jun J. Yang

NCI R01 - \$61,087 - 05/2022 - 04/2023  
Understanding the Increased Risk of Childhood Acute Lymphoblastic Leukemia in Latinos

### Jun J. Yang

Takeda - \$270,377 - 12/2021 - 06/2023  
Preclinical Evaluation of Ponatinib in T-cell Acute Lymphoblastic Leukemia

### Jun J. Yang

AstraZeneca - \$161,070 - 05/2022 - 04/2024  
Combination therapy with BH3 mimetics for T-cell acute lymphoblastic leukemia

### Jun J. Yang

NCI R01 - \$619,047 - 07/2021 - 06/2022  
Biomarkers of dasatinib response and resistance in T-cell acute lymphoblastic leukemia

### Jun J. Yang

NCI U01 - \$119,197 - 09/2021 - 08/2022  
Clonal Therapy for Pediatric T-cell Acute Lymphoblastic Leukemia

## Other Active funding FY2022

### Kelly Caudle

NHGRI U24 - \$934,797  
Clinical Pharmacogenetics Implementation Consortium (CPIC)

### Mark Leggas

NIH R01 - \$230,294  
Mechanistic and Pharmacologic Studies of Selective Mithramycin Analogues Targeting EWS-FLI1 in Ewing Sarcoma

### P. David Rogers

NIAID R01 - \$147,558  
Non-cyp51A-mutation Mediated Triazole Resistance in *Aspergillus fumigatus*

### P. David Rogers

NIAID R01 - \$23,326  
Antifungal antagonism as a cause of treatment failure for invasive mycoses

### Daniel Savic

NCI R01 - \$486,113  
Characterizing noncoding GWAS variants in acute lymphoblastic leukemia treatment outcome

### John Schuetz

NCI R01 - \$386,372  
Transporters and Medulloblastoma

### John Schuetz

NIH R01 - \$26,742  
Inhibition of Apical cAMP/cGMP transporter (MRP4) in Gut Induces Diarrhea

### John Schuetz

NIH R01 - \$26,742  
Inhibition of Apical cAMP/cGMP transporter (MRP4) in Gut Induces Diarrhea

### Clinton Stewart

Pfizer ONITT - \$18,316  
A randomized phase i/ii study of Onivyde in combination with Talazoparib or Temozolomide in Children and Young Adults with Recurrent Solid Malignancies and Ewing Sarcoma (ONITT)

### Clinton Stewart

Ipsen ONITT - \$26,688  
A randomized phase i/ii study of Onivyde in combination with Talazoparib or Temozolomide in Children and Young Adults with Recurrent Solid Malignancies and Ewing Sarcoma (ONITT)

### Clinton Stewart

Novartis - \$67,898  
Novartis CLEE011XUS39T SJDawn

### Clinton Stewart

NCI P30 - \$294,653  
CCSG - Pharmacokinetics Shared Resources

### Jun J. Yang

NIH R03 - \$187,228  
Systems biology analyses to identify driver genes in Down Syndrome-related ALL

### Jun J. Yang

NIH R01 - \$67,206  
Admixture analysis of acute lymphoblastic leukemia in African American children: the ADMIRAL Study

### Jun J. Yang

NIH R01 - \$136,591  
Predictors of Systemic Exposure to Oral 6MP During Maintenance in Adolescents and Young Adults with Acute Lymphoblastic Leukemia (Wolfson)

### Jun J. Yang

NCI R01 - \$124,582  
Pathogenesis of ETV6-Related Acute Lymphoblastic Leukemia Yang Component B - Resubmission

### Jun J. Yang

NIGMS R35 - \$516,960  
Pharmacogenomics of Nucleobase and Nucleoside Analog Drugs

### Jun J. Yang

NCI R01 - \$132,094  
Molecular Epidemiology of ALL in Children with Down Syndrome

### Jun J. Yang

NIH R01 - \$66,666  
Global Disparities in Pediatric Acute Lymphoblastic Leukemia (ALL)

### Liqin Zhu

American Cancer Society - \$192,250  
Molecular and cellular mechanisms of liver cancer metastasis

### Liqin Zhu

NCI R21 - \$246,714  
Ribonucleotide Reductase in Hepatoblastoma Progression and Drug Resistance

# HIGHLIGHTED PUBLICATIONS 2021-2022

## Nature Genetics

**Noncoding genetic variation in GATA3 increases acute lymphoblastic leukemia risk through local and global changes in chromatin conformation**

*Nat Genet.* 2022 Feb;54(2):170-179.

Yang H, Zhang H, Luan Y, Liu T, Yang W, Roberts KG, Qian MX, Zhang B, Yang W, Perez-Andreu V, Xu J, Iyyanki S, Kuang D, Stasiak LA, Reshmi SC, Gastier-Foster J, Smith C, Pui CH, Evans WE, Hunger SP, Plataniotis LC, Relling MV, Mullighan CG, Loh ML, Yue F, Yang JJ.

## Journal of the American Medical Association

**Association of Genetic Ancestry With the Molecular Subtypes and Prognosis of Childhood Acute Lymphoblastic Leukemia**

*JAMA Oncol.* 2022 Mar 1;8(3):354-363.

Lee SHR, Antillon-Kluschmann F, Pei D, Yang W, Roberts KG, Li Z, Devidas M, Yang W, Najera C, Lin HP, Tan AM, Ariffin H, Cheng C, Evans WE, Hunger SP, Jeha S, Mullighan CG, Loh ML, Yeoh AEJ, Pui CH, Yang JJ.

## Blood

**Impact of T-cell immunity on chemotherapy response in childhood acute lymphoblastic leukemia**

*Blood.* 2022 Sep 29;140(13):1507-1521.

Li Y, Yang X, Sun Y, Li Z, Yang W, Ju B, Easton J, Pei D, Cheng C, Lee S, Pui CH, Yu J, Chi H, Yang JJ.

## Science Translational Medicine

**Preclinical evaluation of proteolytic targeting of LCK as a therapeutic approach in T cell acute lymphoblastic leukemia**

*Sci Transl Med.* 2022 Aug 24;14(659):eabo5228.

Hu J, Jarusiewicz J, Du G, Nishiguchi G, Yoshimura S, Panetta JC, Li Z, Min J, Yang L, Chepyala D, Actis M, Reyes N, Smart B, Pui CH, Teachey DT, Rankovic Z, Yang JJ.

## Nature Communications

**Epigenetic activation of the FLT3 gene by ZNF384 fusion confers a therapeutic susceptibility in acute lymphoblastic leukemia**

*Nat Commun.* 2022 Sep 14;13(1):5401.

Zhao X, Wang P, Diedrich JD, Smart B, Reyes N, Yoshimura S, Zhang J, Yang W, Barnett K, Xu B, Li Z, Huang X, Yu J, Crews K, Yeoh AEJ, Konopleva M, Wei CL, Pui CH, Savic D, Yang JJ.

## Hepatology

**A developmentally prometastatic niche to hepatoblastoma in neonatal liver mediated by the Cxcl1/Cxcr2 axis**

*Hepatology.* 2022 Nov;76(5):1275-1290.

Fan L, Pan Q, Yang W, Koo SC, Tian C, Li L, Lu M, Brown A, Ju B, Easton J, Ranganathan S, Shin S, Bondoc A, Yang JJ, Yu J, Zhu L.

## Journal of the American Medical Association Network Open

**Association of Inherited Genetic Factors With Drug-Induced Hepatic Damage Among Children With Acute Lymphoblastic Leukemia**

*JAMA Netw Open.* 2022 Dec 1;5(12):e2248803.

Yang W, Karol SE, Hoshitsuki K, Lee S, Larsen EC, Winick N, Carroll WL, Loh ML, Raetz EA, Hunger SP, Winter SS, Dunsmore KP, Devidas M, Relling MV, Yang JJ.

## Clinical Microbiology & Infection

**In vivo emergence of high-level resistance during treatment reveals the first identified mechanism of amphotericin B resistance in *Candida auris***

*Clin Microbiol Infect.* 2022 Jun;28(6):838-843.

Rybak JM, Barker KS, Muñoz JF, Parker JE, Ahmad S, Mokaddas E, Abdullah A, Elhagracy RS, Kelly SL, Cuomo CA, Rogers PD.



# HIGHLIGHTED PUBLICATIONS

## 2021-2022

### Leukemia

#### Epigenomic profiling of glucocorticoid responses identifies cis-regulatory disruptions impacting steroid resistance in childhood acute lymphoblastic leukemia

*Leukemia*. 2022 Oct;36(10):2374-2383.

Bergeron BP, Diedrich JD, Zhang Y, Barnett KR, Dong Q, Ferguson DC, Autry RJ, Yang W, Hansen BS, Smith C, Crews KR, Fan Y, Pui CH, Pruett-Miller SM, Relling MV, Yang JJ, Li C, Evans WE, Savic D.

### Journal of the National Cancer Institute

#### Molecular Mechanisms of ARID5B-Mediated Genetic Susceptibility to Acute Lymphoblastic Leukemia

*J Natl Cancer Inst*. 2022 Sep 9;114(9):1287-1295.

Zhao X, Qian M, Goodings C, Zhang Y, Yang W, Wang P, Xu B, Tian C, Pui CH, Hunger SP, Raetz EA, Devidas M, Relling MV, Loh ML, Savic D, Li C, Yang JJ.

### Haematologica

#### Comprehensive analysis of dose intensity of acute lymphoblastic leukemia chemotherapy

*Haematologica*. 2022 Feb 1;107(2):371-380.

Karol SE, Pei D, Smith CA, Liu Y, Yang W, Kornegay NM, Panetta JC, Crews KR, Cheng C, Finch ER, Inaba H, Metzger ML, Rubnitz JE, Ribeiro RC, Gruber TA, Yang JJ, Evans WE, Jeha S, Pui CH, Relling MV.

### British Journal of Haematology

#### Low NUDT15 expression levels due to biallelic NUDT15 variants and 6-mercaptopurine intolerance

*Br J Haematol*. 2022 Oct;199(2):270-276.

Yoshida M, Brown SA, Moriyama T, Nishii R, Tsujimoto SI, Yamada Y, Yoshida K, Shirai R, Osumi T, Utano T, Fukano R, Kudo K, Sakaguchi K, Arakawa Y, Koh K, Sekiguchi M, Sekimizu M, Miyamura T, Ishida H, Inukai T, Tomizawa D, Kiyokawa N, Kato M, Yang JJ.

### Blood Advances

#### Identification of TCF3 germline variants in pediatric B-cell acute lymphoblastic leukemia

*Blood Adv*. 2022 Dec 28;bloodadvances.2022008563.

Escherich CS, Chen W, Miyamoto S, Namikawa Y, Yang W, Teachey DT, Li Z, Raetz EA, Larsen EC, Devidas M, Martin PL, Bowman WP, Wu G, Pui CH, Hunger SP, Loh ML, Takagi M, Yang JJ.

### Blood Advances

#### Amino acid stress response genes promote L-asparaginase resistance in pediatric acute lymphoblastic leukemia

*Blood Adv*. 2022 Jun 14;6(11):3386-3397.

Ferguson DC, McCorkle JR, Barnett KR, Bonten EJ, Bergeron BP, Bhattarai KR, Yang W, Smith C, Hansen BS, Bajpai R, Dong Q, Autry RJ, Gocho Y, Diedrich JD, Crews KR, Pruett-Miller SM, Roberts KG, Stock W, Mullighan CG, Inaba H, Jeha S, Pui CH, Yang JJ, Relling MV, Evans WE, Savic D.

### Blood Advances

#### Genome-wide CRISPR/Cas9 screening identifies determinant of panobinostat sensitivity in acute lymphoblastic leukemia

*Blood Adv*. 2022 Apr 26;6(8):2496-2509.

Jiang C, Qian M, Gocho Y, Yang W, Du G, Shen S, Yang JJ, Zhang H.

### Antimicrobial Agents & Chemotherapy

#### Candida parapsilosis Mdr1B and Cdr1B Are Drivers of Mrr1-Mediated Clinical Fluconazole Resistance

*Antimicrob Agents Chemother*. 2022 Jul 19;66(7):e0028922.

Doorley LA, Rybak JM, Berkow EL, Zhang Q, Morschhäuser J, Rogers PD.

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