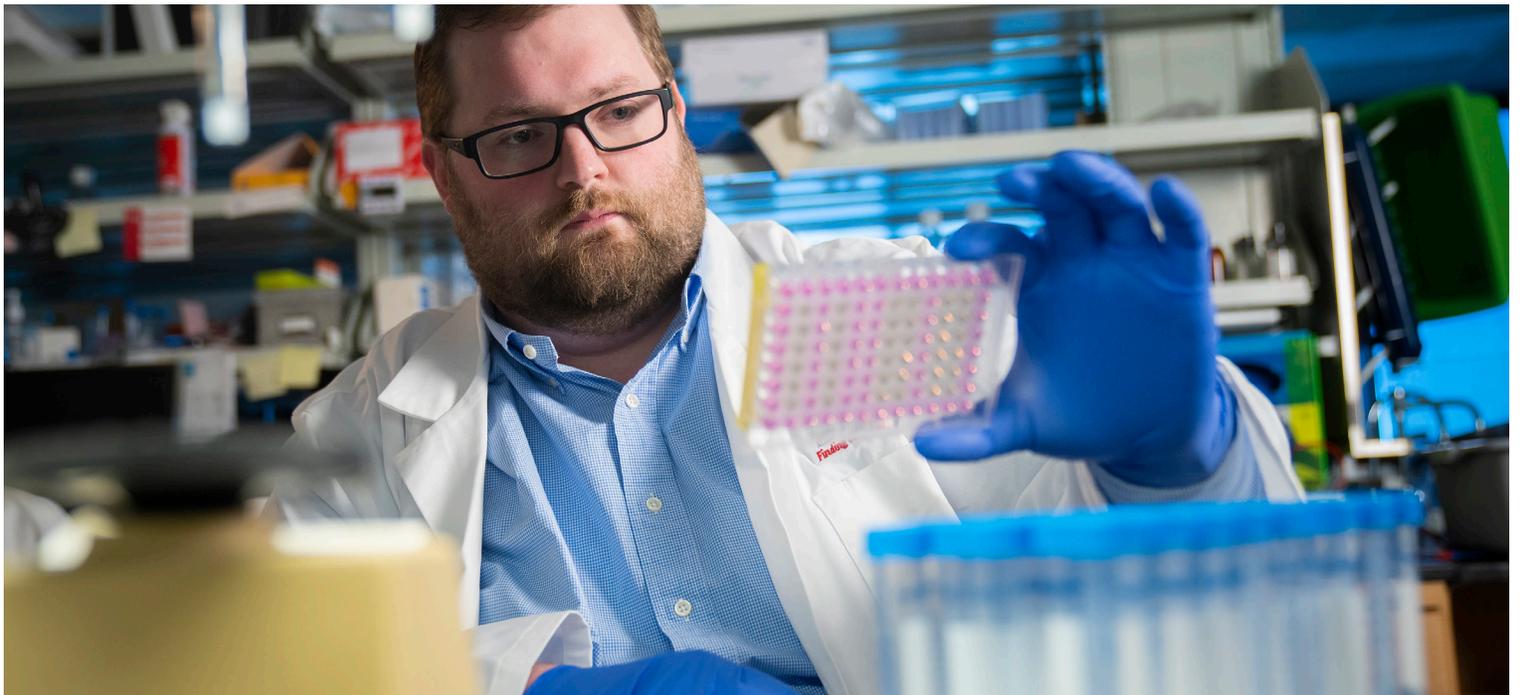


DEPARTMENT OF PHARMACEUTICAL SCIENCES



St. Jude Children's
Research Hospital
Finding cures. Saving children.
ALSAC • DANNY THOMAS, FOUNDER



ANNUAL REPORT 2020

DEPARTMENT OF PHARMACEUTICAL SCIENCES

FACULTY:

Full Members: William E. Evans, Pharm.D.; William Greene, Pharm.D.; James M. Hoffman, Pharm.D., M.S.; Mary V. Relling, Pharm.D. (chair); P. David Rogers, Pharm.D., Ph.D., (chair); Erin G. Schuetz, Ph.D.; John D. Schuetz, Ph.D. (vice-chair); Clinton F. Stewart, Pharm.D.; Jun J. Yang, Ph.D.

Assistant Members: Daniel Savic, Ph.D.; Liqin Zhu, Ph.D.

Instructor: Jeffrey Rybak, Pharm.D., Ph.D.

CLINICAL LABORATORY DIRECTORS:

Alejandro Molinelli, Ph.D.; Kristine R. Crews, Pharm.D.; Clinton F. Stewart, Pharm.D.

POSTDOCTORAL FELLOWS:

Stefanie Baril, Ph.D.; Jordan Beard, Ph.D.; Christian DeJarnette, Ph.D.; Jonathan Diedrich, Ph.D.; Qian (Jessie) Dong, Ph.D.; Li Fan, Ph.D.; Daniel Ferguson, Ph.D.; Emily Finch, Ph.D.; Elizabeth Gibson, Pharm.D., Ph.D.; Tomoka Gose, Ph.D.; Joshua Hess, M.D.; Yizhen Li, Ph.D.; Yiwei Liu, Ph.D.; Takaya Moriyama, M.D., Ph.D.; Rina Nishii, Ph.D.; Sabina Ranjit, Ph.D.; Wentao Yang, Ph.D.; Jingliao Zhang, Ph.D.

PHARMACY RESIDENTS:

Chelsea Drennan, Pharm.D.; Jaclyn Hopp, Pharm.D.; Deann Tims, Pharm.D.; Katherine Robinson, Pharm.D.

GRADUATE STUDENTS:

Kavya Annu, R.J. Autry, Brennan Bergeron, Anthony Brown, Tyler Dunn, Laura Doorley, Jianzhong Hu, Yu Li, Joseph Miller, Xujie Zhao, Jingwen Zhu, Chan Zou

INFORMATICS STAFF:

Nancy Kornegay, Andrey Matlin, Claire Mills, Ben McKinley, Carl Panetta, Ph.D., Colton Smith, Ph.D., Wenjian Yang, Ph.D.

STAFF SCIENTISTS:

Kathy Barker, Ph.D.; Erik Bonten, Ph.D.; Amarjit Chaudhry, Ph.D.; Barthelémy Diouf, Ph.D.; Yu Fukuda, Ph.D.; John Lynch, Ph.D.; Ana Oliveira Souza, Ph.D.

PHARMACY LEADERSHIP:

David Aguero, Pharm.D.; Cindy Brasher, Pharm.D.; Delia Carias, Pharm.D.; Kelly Caudle, Pharm.D., Ph.D.; Wendell Cheatham, D.Ph.; Cyrine Haidar, Pharm.D.; William Humphrey, D.Ph., M.S., M.B.A.; John McCormick, Pharm.D.; Steve Pate, D.Ph.; Jennifer Pauley, Pharm.D.; Jennifer Robertson, Pharm.D.; Cheri Wilkerson, Pharm.D.; Barry Williams, B.S. Pharm.

CLINICAL PHARMACY SPECIALISTS:

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

PHARMACISTS:

Chris Askins, Pharm.D.; Amy Bass, Pharm.D.; Robert Bruno, Pharm.D.; Susan Carr, Pharm.D.; Robbin Christensen, B.S. Pharm.; Richard Clark, Pharm.D.; Clay Daniels, Pharm.D., Ph.D.; Hana Danzi, M.S., Pharm.; Nousheen DeRenzo, Pharm.D.; Maureen Esposito, Pharm.D.; Debra Ethridge, Pharm.D.; Joseph Evans, Pharm.D.; Liz Gallimore, Pharm.D.; Kristen Hughes, Pharm.D.; Nevonda Jackson, Pharm.D.; Jennifer Kemper, Pharm.D.; Jenny Knych, Pharm.D.; Chuck Longserre, Pharm.D.; Shane Marshall, Pharm.D.; Jennifer Mason, Pharm.D.; Anne McCormick, B.S. Pharm.; Tommy Mills, Pharm.D.; Ben Moore, Pharm.D.; Heather Mullins, Pharm.D.; Tiffany Nason, Pharm.D.; Monica Patel, Pharm.D.; Trina Peery, Pharm.D.; Jackie Quackenbush, B.S. Pharm.; Julie Richardson, Pharm.D.; Chris Scobey, Pharm.D.; Camille Smith, Pharm.D.; Kevin Smith, Pharm.D.; Tabetha Todd, Pharm.D.; Dagny Ulrich, Pharm.D.; Gayle Westmoreland, B.S. Pharm.; Curtis Yeh, Pharm.D.; Keith Young, B.S. Pharm., RJ Zarkani, Pharm.D.

BY THE NUMBERS

12

faculty members

35

Ph.D. scientists

18

post-doctoral fellows

12

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

2

Fellows of the American Society of Health-System Pharmacists



88

total publications

63

publications from Pharmaceutical Sciences

25

publications from Pharmaceutical Services

6.0

median journal impact factor

22

publications in journals with an impact factor of >10

\$7,402,255

grant funding/active extramural funding

\$6,591,252

total active NIH funding

THE OVERALL MISSION OF THE DEPARTMENT OF PHARMACEUTICAL SCIENCES

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 of Pharmaceutical Sciences comprises Pharmaceutical Sciences (with a primary mission of research), and Pharmaceutical Services (with a primary mission of clinical care). Both research and treatment are highly intertwined at St. Jude Children's Research Hospital, and this integration exists within other academic departments at SJCRH that have a dual mission of patient care and research. Many of our departmental faculty and staff members are extensively involved in both research and patient care. Indeed, the synergies and efficiencies of having the research and service components in a single academic department have been hallmarks of SJCRH since it was established in 1962 and facilitates the success of our institution.

Our vision is to be a premier academic department in pharmacy and pharmaceutical sciences, 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 less than optimal use of medications. Our goal is to elucidate the biological basis of interindividual 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 nongenetic 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 (*see Figure 1*). Laboratory work informs clinical studies and clinical problems drive much of our laboratory work.

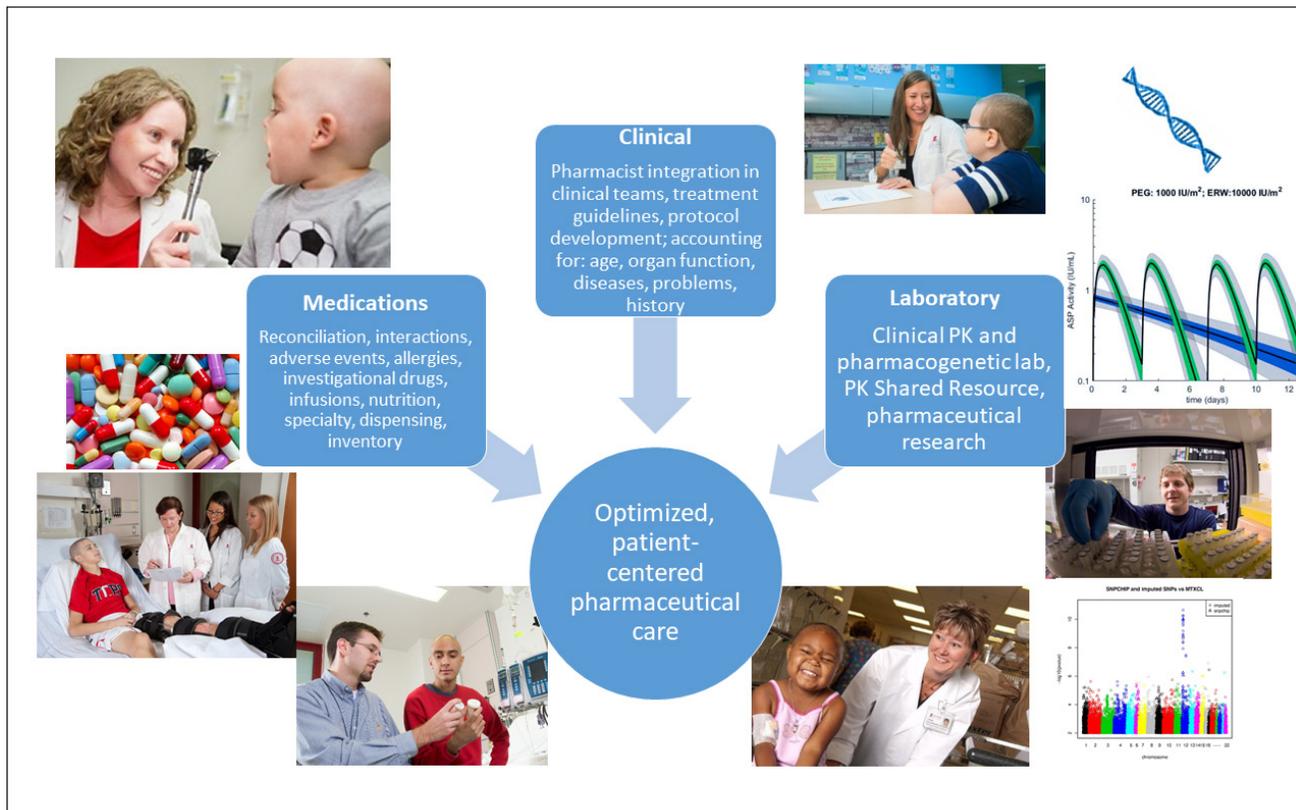


Figure 1. With responsibility for medications, the use of clinical data, and the development of clinical and research laboratory tests, knowledge is used to provide the best possible care for St. Jude patients while also making discoveries with implications outside of St. Jude.

Faculty members lead and participate in interdisciplinary St. Jude programs and national cooperative research collaborations. Our pharmacogenetic research integrates genome-wide analyses, molecular analyses, functional genomics, pharmacokinetics, and pharmacodynamics to identify genetic determinants of drug effects, with the long-term goal of optimizing therapy for individual patients.

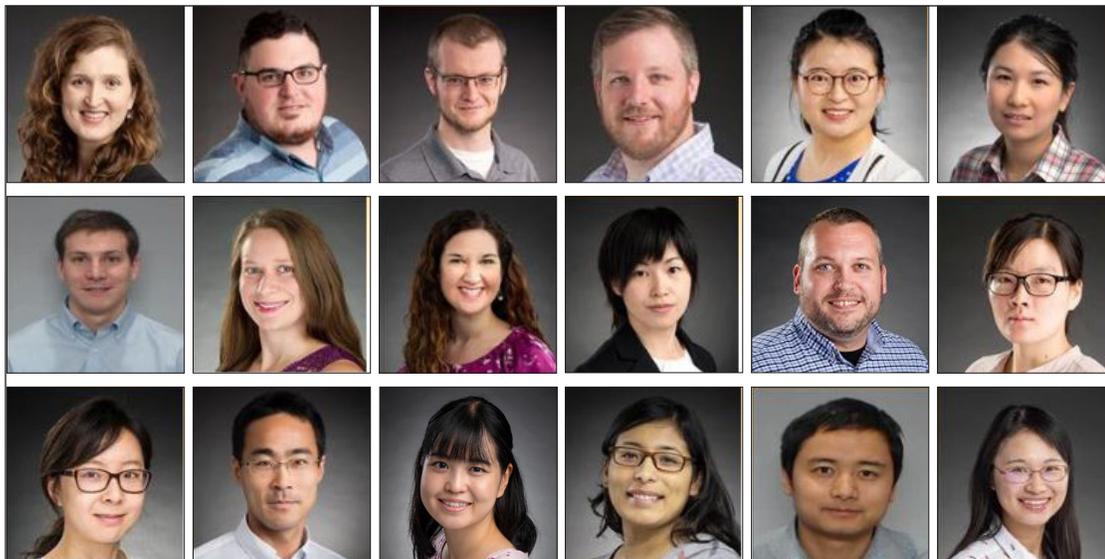


Figure 2. Post-doctoral fellows 2019-2020: Stefanie Baril, Ph.D.; Jordan Beard, Ph.D.; Christian DeJarnette, Ph.D.; Jonathan Diedrich, Ph.D.; Qian (Jessie) Dong, Ph.D.; Li Fan, Ph.D.; Daniel Ferguson, Ph.D.; Emily Finch, Ph.D.; Elizabeth Gibson, Pharm.D., Ph.D.; Tomoka Gose, Ph.D.; Joshua Hess, M.D.; Yizhen Li, Ph.D.; Yiwei Liu, Ph.D.; Takaya Moriyama, M.D., Ph.D.; Rina Nishii, Ph.D.; Sabina Ranjit, Ph.D.; Wentao Yang, Ph.D.; Jingliao Zhang, Ph.D.

The Department has twelve faculty members, 15-25 post-doctoral fellows (**see Figure 2**) 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 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. Pharmaceutical Sciences occupies over 15,000 sq. ft. of contiguous state-of-the-art equipped laboratory and office space, and Pharmaceutical Services occupies over 18,000 square feet of space in the clinical areas of St. Jude. The department hosts weekly research workshops and journal clubs that are open to the entire institution which are widely attended by colleagues outside the department. As well as multiple laboratory and services specific meetings, webinars with national and international colleagues, and regular pharmacogenomics meetings.

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

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

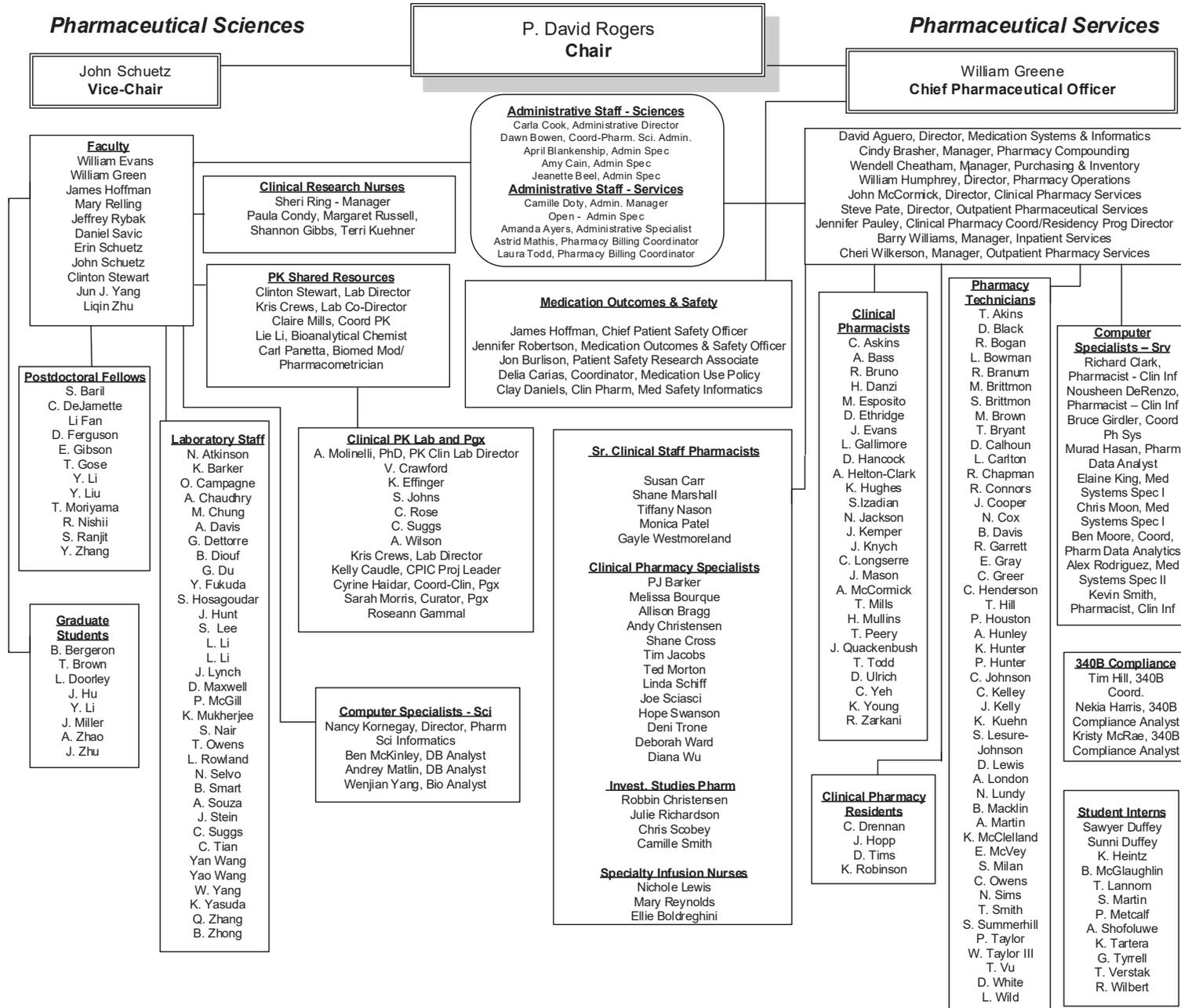
While the COVID-19 pandemic brought unexpected challenges to the department in 2020, our faculty, pharmacists, and staff continued undeterred in our efforts for the patients we serve. This year also saw change in departmental leadership with Dr. Mary Relling stepping down as Chair of the Department of Pharmaceutical Sciences. Dr. Clinton Stewart served as Interim Chair during the transition between leadership, and Dr. David Rogers was recruited to serve as the new Chair in August.



Dr. David Rogers was named Chair of the Department of Pharmaceutical Sciences in August.

ORGANIZATIONAL CHART

ST. JUDE CHILDREN'S RESEARCH HOSPITAL – Department of Pharmaceutical Sciences





WILLIAM E. EVANS, PHARM.D.

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 (**see Figure 3 below**) (*Holleman, NEJM 2004; Lughart, 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 (*Diouf, JAMA 2015; Paugh*

et al, Nat Genet 2015) of antileukemic agents as well as the influence of somatic and karyotypic abnormalities on genotype-phenotype concordance (*Cheng, Nature Genet 2005; Diouf et al, Nature Med 2011*). Having previously identified high CASP1/NLRP3 expression as a mediator of glucocorticoid resistance (*Paugh et al, 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 enhance GR function and leukemia cell response to glucocorticoids in *ex vivo* and *in vivo* models and in primary ALL cells from patients.

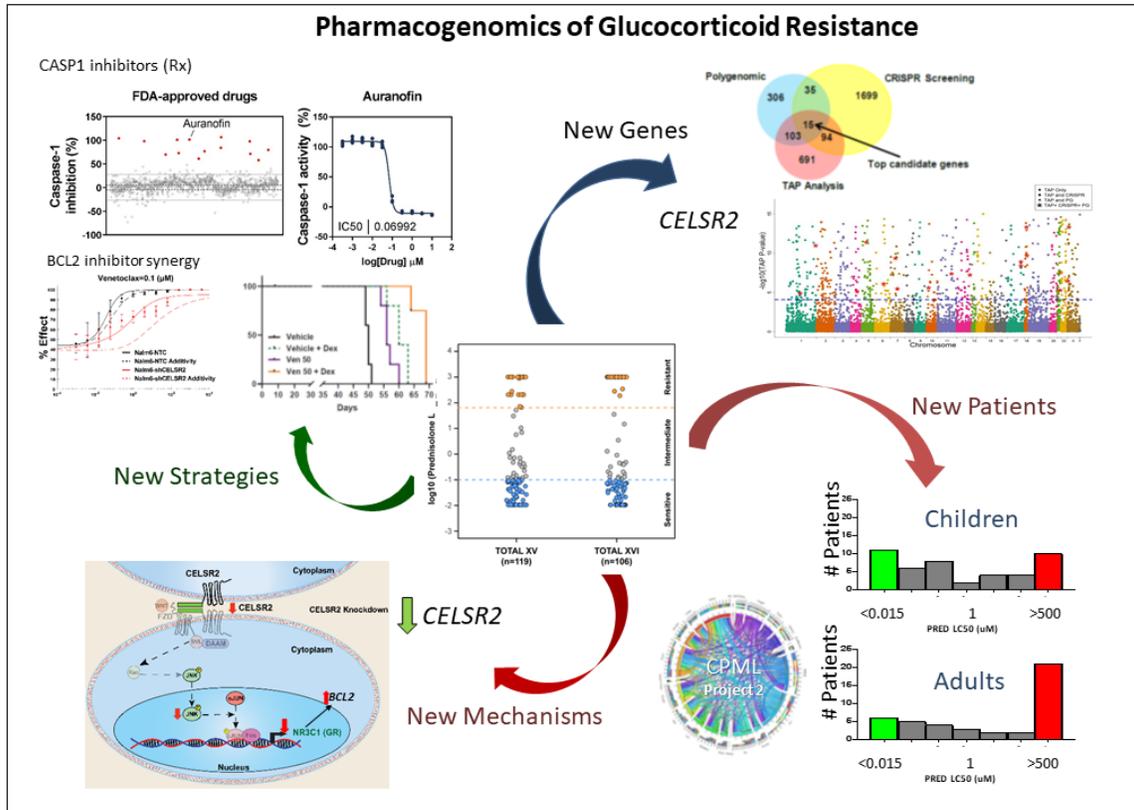


Figure 3. In work supported by the NIH funded Center for Precision Medicine in Leukemia, we have initially focused on identifying mechanisms by which primary acute lymphoblastic leukemia (ALL) cells are resistant to chemotherapy, at the time of initial diagnosis (i.e., *de novo* resistance). Our initial 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, CELSR2, 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 CELSR2 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.



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

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

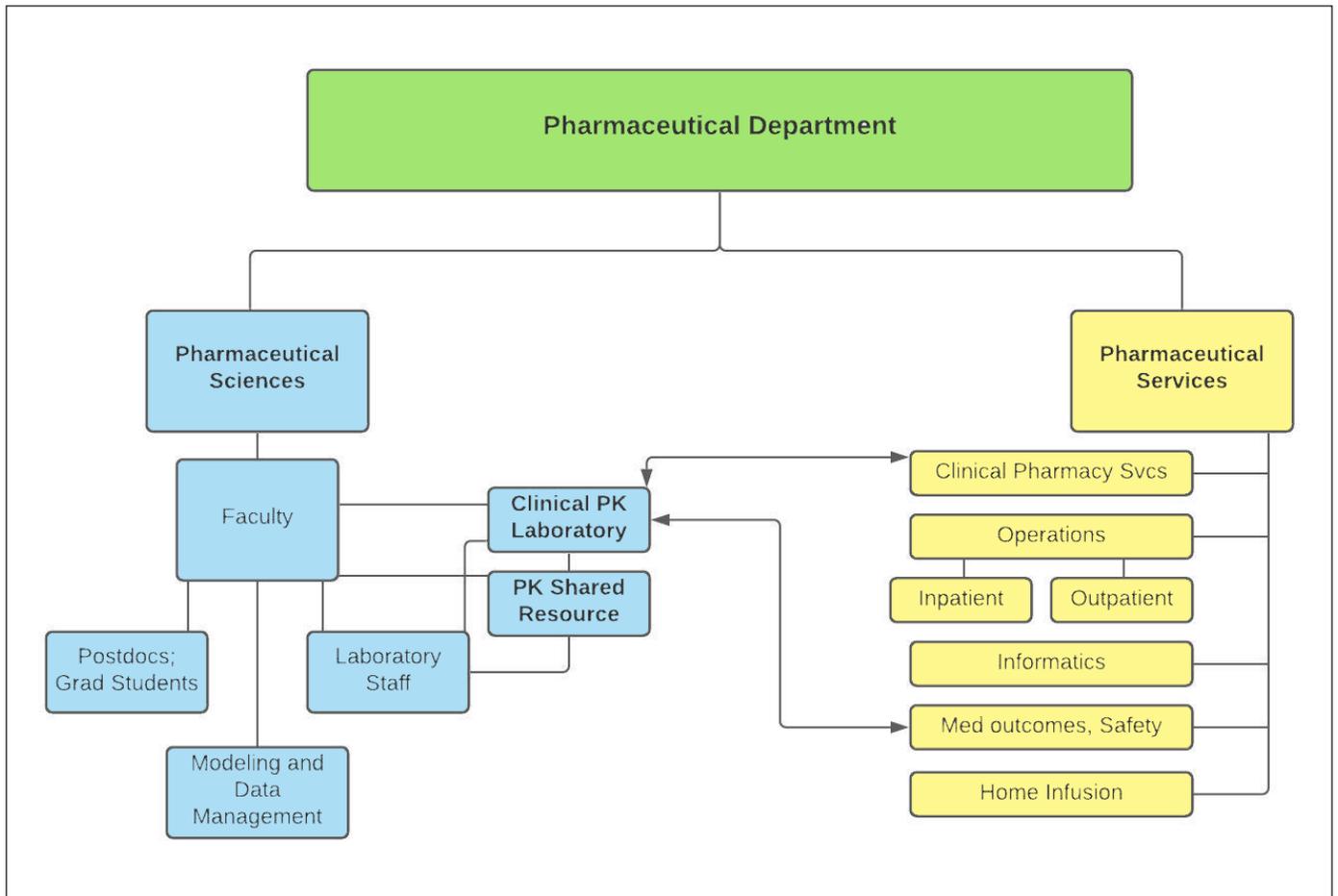


Figure 4. Functional interplay between pre-clinical and clinical sections in the department



JAMES M. HOFFMAN, PHARM.D., M.S.

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 (*see Figure below*), 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) 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](#)).

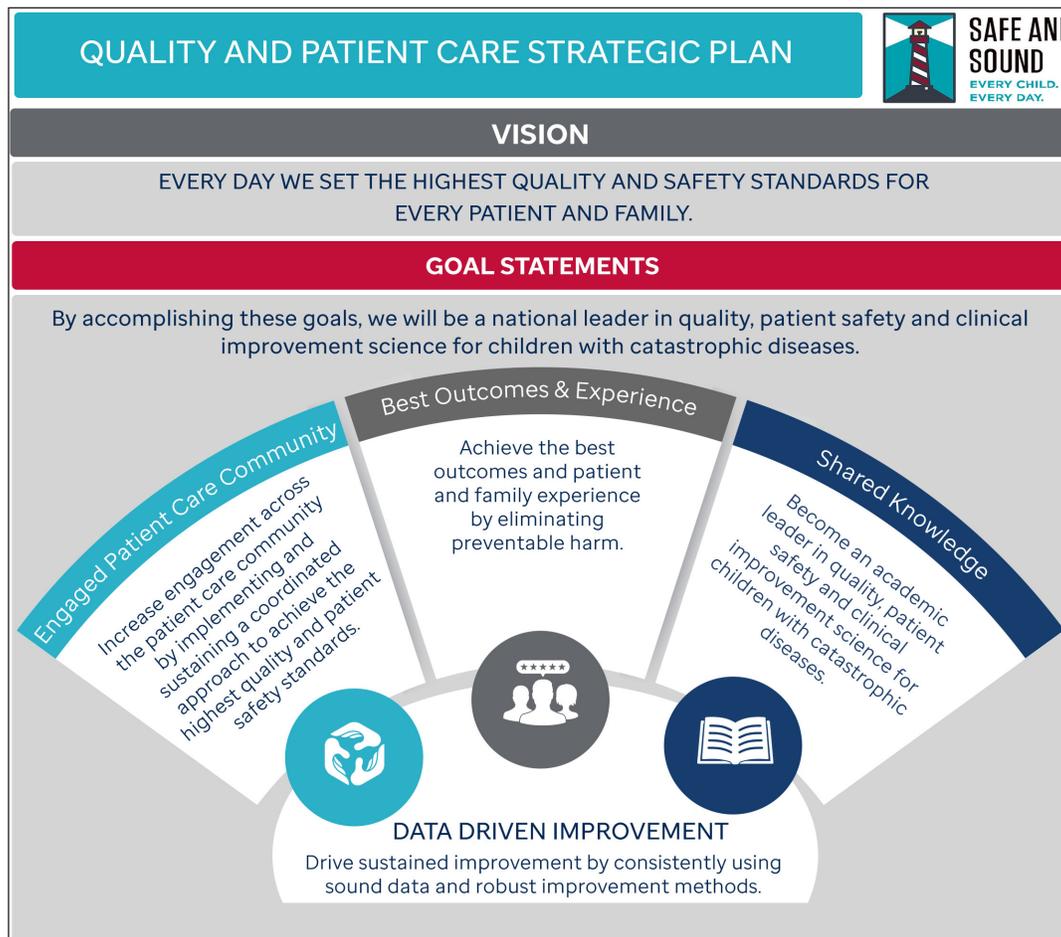
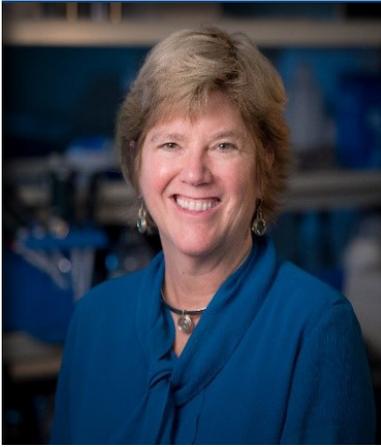


Figure 5.



MARY V. RELING, PHARM.D.

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

The ALL phenotypes we focus on most include relapse, glucocorticoid induced osteonecrosis, asparaginase immunogenicity (**see Figure 6 below**) and pharmacodynamics, and hepatotoxicity (e.g. Liu Y et al, *JCO*, 2019 and *Blood* 2020, Finch et al *Haematologica* 2020). Our laboratory has a heavy reliance on computational approaches, as we use genome-wide tools to interrogate genetic variability.

In addition to discovery research, we lead work to implement preemptive clinical pharmacogenomic testing. This is accomplished locally at St. Jude via a clinical protocol, PG4KDS (www.stjude.org/pg4kds) and internationally via the Clinical Pharmacogenetics Implementation Consortium (CPIC®, www.cpicpgx.org) (Caudle et al *Genet Med* 2017), an NIH-supported genomics resource. Our staff help lead efforts to create and curate gene/drug pair CPIC prescribing guidelines. St. Jude played a leading role in the recent update of the CPIC guideline for thiopurines, which now includes NUDT15 in addition to TPMT (Relling et al *Clin Pharmacol Ther* 2018). We collaborate with many investigators within the department, throughout St. Jude, within the COG, and within the Pharmacogenomics Research Network (PGRN).

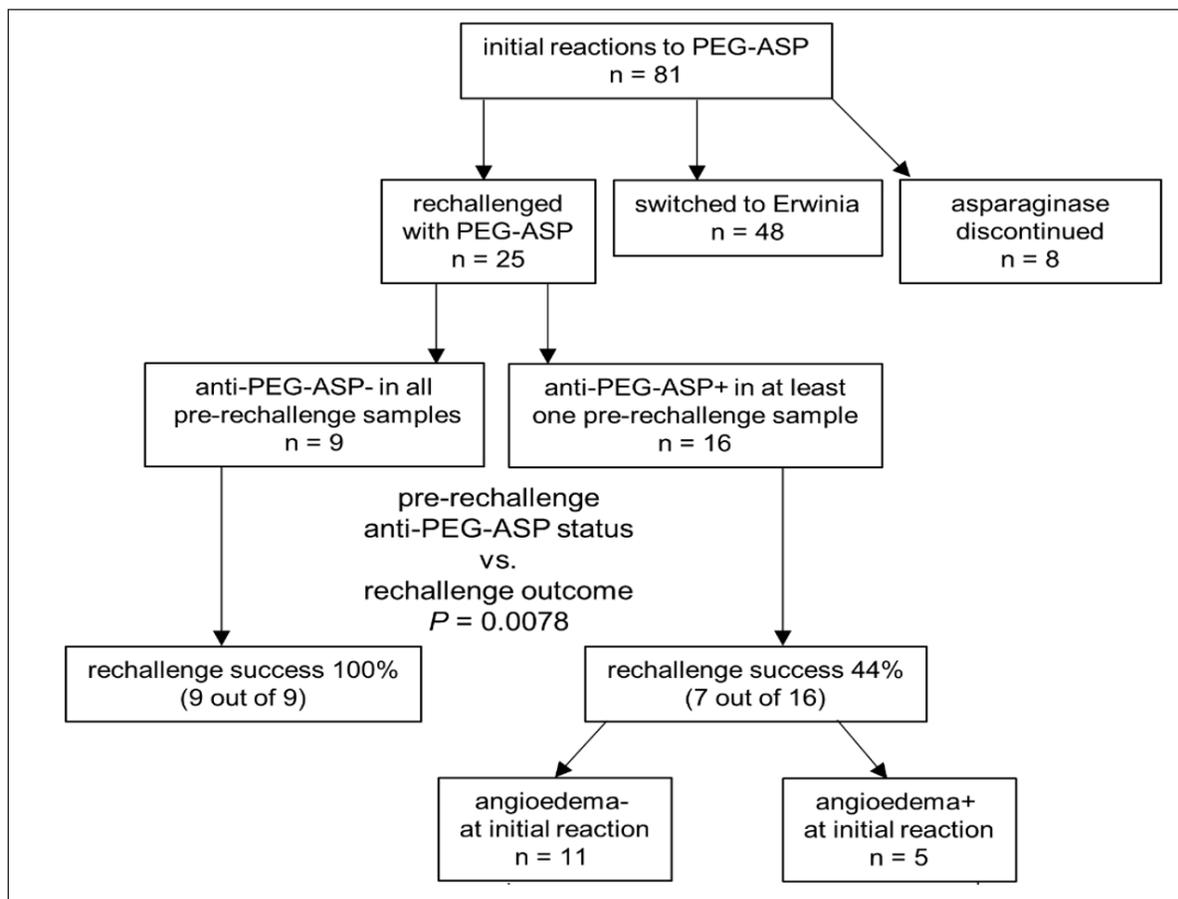


Figure 6. We developed and validated a CLIA-compliant assay for anti-PEG-ASP (anti polyethylene-glycol conjugated asparaginase) in sera of patients with ALL, which is now used routinely in St. Jude patients. In multivariate analysis, the presence of anti-PEG-ASP ($p = 0.027$) and angioedema ($p = 0.01$) both predicted failure of rechallenge with further PEG-ASP doses. The majority of patients reacting to PEG-ASP are in fact reacting to the PEG, not to the asparaginase enzyme (Liu et al, *J Clinical Oncol*, 2019).

P. DAVID ROGERS, PHARM.D., PH.D.



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, all with limitations. Moreover, resistance to these antifungals has become a significant 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 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 agent in pathogenic fungi (overviewed in **Figure 7**). 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). Work is also underway to understand the molecular and genetic basis of multidrug resistance in the emerging fungal pathogen *C. auris* as well as triazole resistance in the mold *Aspergillus fumigatus* by mapping the genomes of clinical isolates. Here we have recently discovered that activating mutations in the gene encoding the transcription factor Tac1b is a major driver of fluconazole resistance in the former (Rybak, mBio 2020), whereas mutations in the region encoding the sterol sensing domain of HMG-CoA reductase are a novel driver of triazole resistance in the latter (Rybak, mBio 2019).

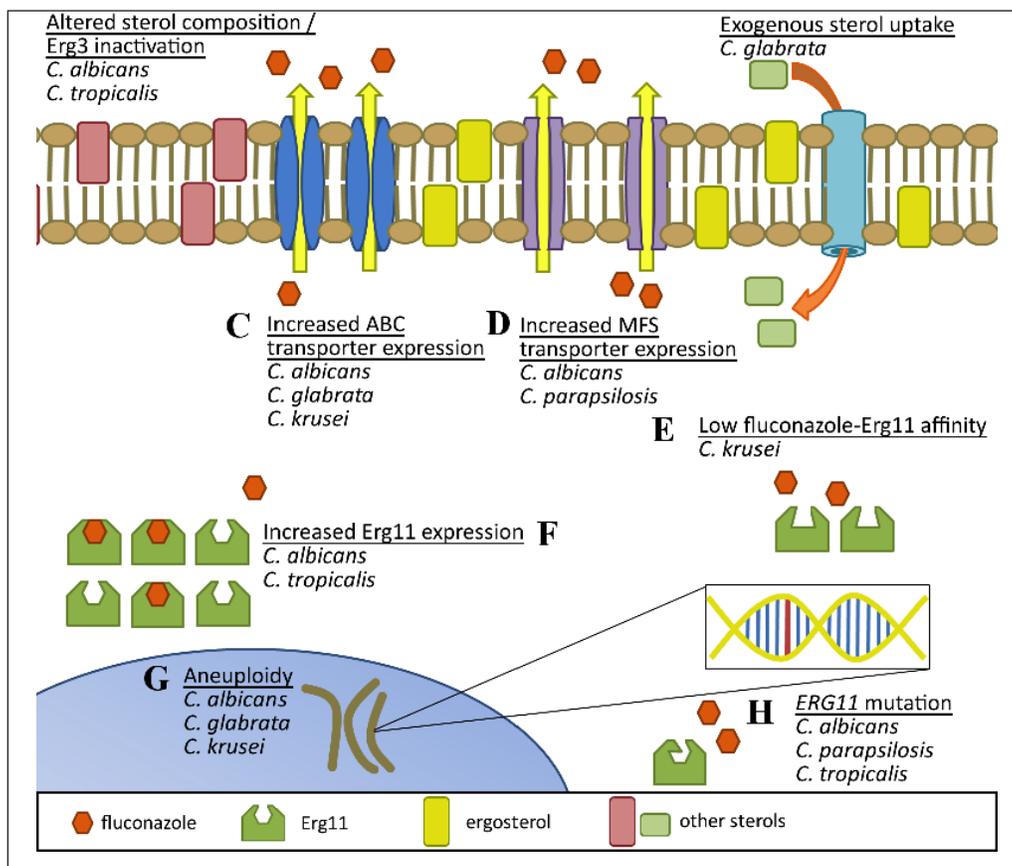


Figure 7. Comparison of documented fluconazole resistance mechanisms in *Candida* species. A) Erg3 inactivation results in utilization of alternative sterols in the yeast membrane. B) Uptake of exogenous sterols helps circumvent endogenous sterol production inhibition by fluconazole. Increased production 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.



I joined the faculty of the Department of Pharmaceutical Sciences at St. Jude Children's Research Hospital as an Instructor in September of 2020. Previously, my 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).

My 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, my lab is currently working to identify and characterize novel *C. auris* regulators of antifungal stress response which can be exploited as molecular vulnerabilities and targeted to enhance the activity of clinically available antifungal agents. My preliminary studies have identified genes encoding transcriptional regulators which are differentially expressed in response to antifungal treatment, and I have observed that loss of certain of these transcriptional regulators confer hyper-susceptibility to antifungal agents. I am currently working to characterize the downstream targets of these transcriptional regulators and define those which may be exploited as co-therapeutic targets. In addition to my benchtop research, I am also a member of the Antimicrobial Utilization and Improvement Committee (AUC).

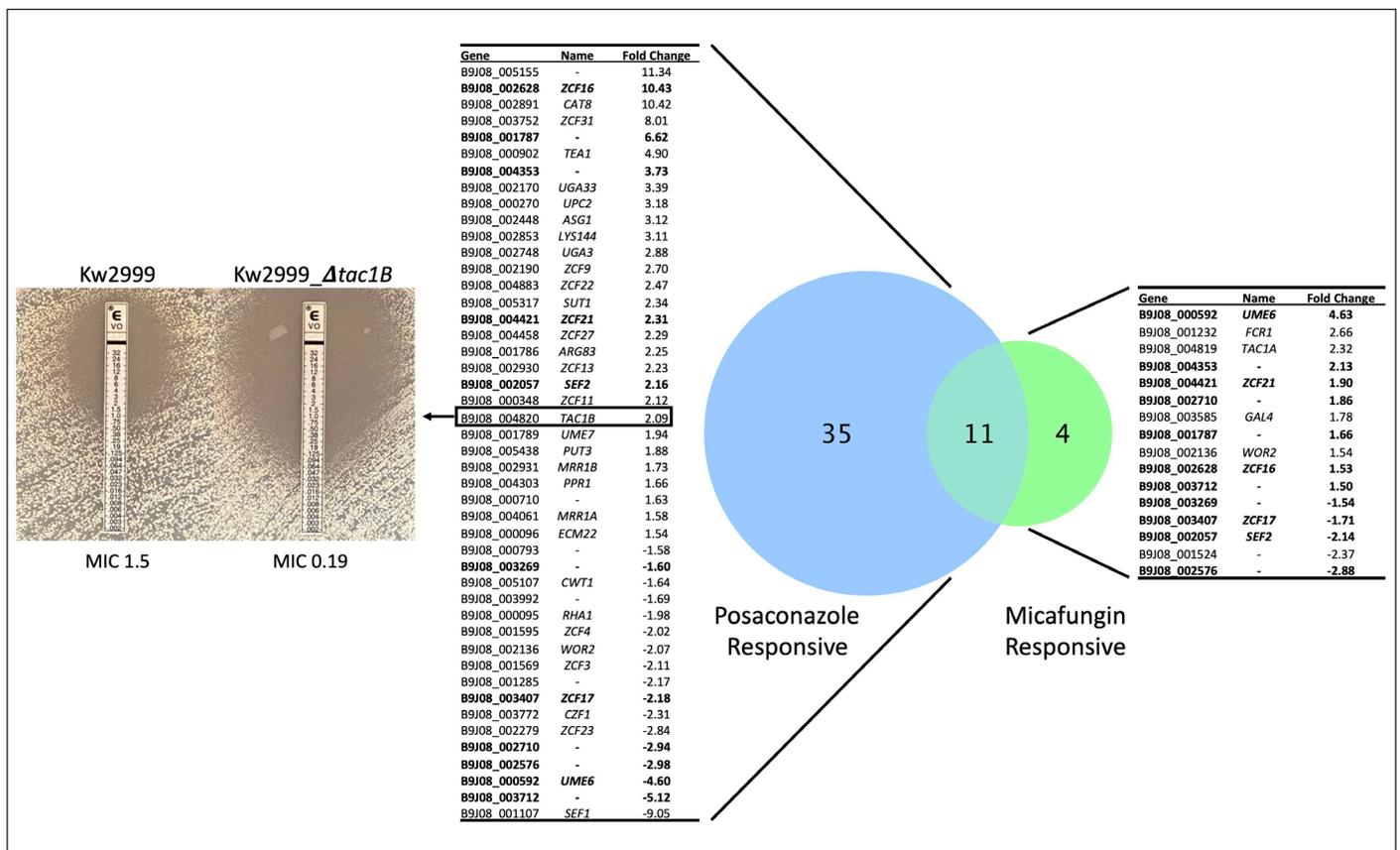


Figure 8.

***Candida auris* Zinc cluster transcription factor (ZCF) genes are expressed differentially in response to antifungal drug exposure and genetic depletion of certain of these genes confer enhanced susceptibility to clinically available antifungal drugs.** Genes shown are those predicted to encoding ZCF which were observed to be differentially expressed (≥ 1.5 -fold; $FDR \leq 0.01$) in the pan-antifungal resistant *C. auris* clinical isolate Kw2999 in response to pharmacologically relevant concentrations of either posaconazole (1mg/L) or micafungin (4mg/L) as compared to DMSO-only controls. Genes in bold were differentially expressed in response to both posaconazole and micafungin treatment. Voriconazole MIC for clinical isolate Kw2999 and the *TAC1B* disruption strain, Kw2999_Δ*tac1B*, as determined by Etest.



ERIN G. SCHUETZ, PH.D.

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 have been developing **novel pre-clinical screening models**. Animal models have been used for years to describe/predict xenobiotic disposition in humans but frequently fail because the activity levels of ADME genes, including transporters, do not mirror what occurs in humans. **Indeed, we identified major species differences between rodents and humans in expression of MDR1/P-glycoprotein at the choroid plexus (CP) – specifically humans express Pgp at the CP, while mice do not.** The implications of this species difference are numerous. If a chemotherapeutic drug found effective for treating ependymal tumors is a Pgp substrate, it would fail in preclinical trials in

conventional mice models of these tumors because blood brain barrier (BBB) Pgp blocks drug entry to the brain, and mice lack CP Pgp. However, it might work in humans because CP Pgp expression would enforce blood→CSF drug movement. **Hence, we developed and characterized a novel transgenic (TG) mouse expressing CP Pgp.** The functionality of Pgp in the CP of TG mice was verified using its ability to efflux Rhodamine 800 (Rho800), a fluorescent PGP substrate. Thirty minutes after intravenous administration of Rho800 to mice, Rho800 fluorescence was found to be lower in the excised CP tissues of TG mice, compared to WT mice (*see Figure 9*). In addition, ex vivo incubation of CP tissues from TG mice with 5 μ M Rho800 for 30 mins exhibited decreased Rho800 fluorescence, compared to those from WT mice, which was reversed by pre-treatment of the CP tissues with 5 μ M Cyclosporine A (a Pgp inhibitor) in the TG, but not WT mice (*see Figure 10*). To assess the effect of CP Pgp on systemic to CSF movement of substrates we are currently collaborating with Dr. Clinton Stewart who uses microdialysis to measure the effect of CP Pgp expression on blood to CSF movement of methotrexate. Future experiments are planned to determine whether the CSF disposition of Pgp substrates used to treat ependymoma (e.g., Ribociclib) in SJDAWN, is affected by CP Pgp in the transgenic mice. If, as expected, we see significantly improved delivery into the CSF of Pgp substrates in CP-Pgp mice, we would plan to test whether treatment with ribociclib, currently regarded as BBB non-penetrating (due to BBB Pgp), is effective in a mouse model of ependymal tumors with CP Pgp expression.

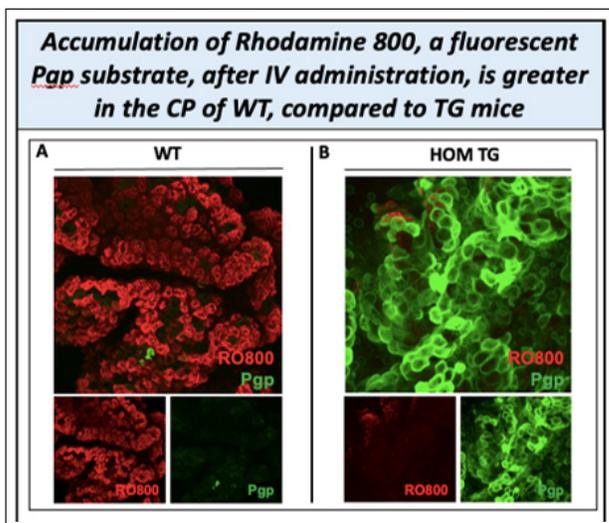


Figure 9. Rhodamine 800 (Rho800) fluorescence, indicating its accumulation, is greater in the CP of (A) WT, compared to (B) Homozgous CP- Pgp-EGFP TG mice, after IV administration of Rho800 and fluorescence imaging of excised CP tissues 30 min later.

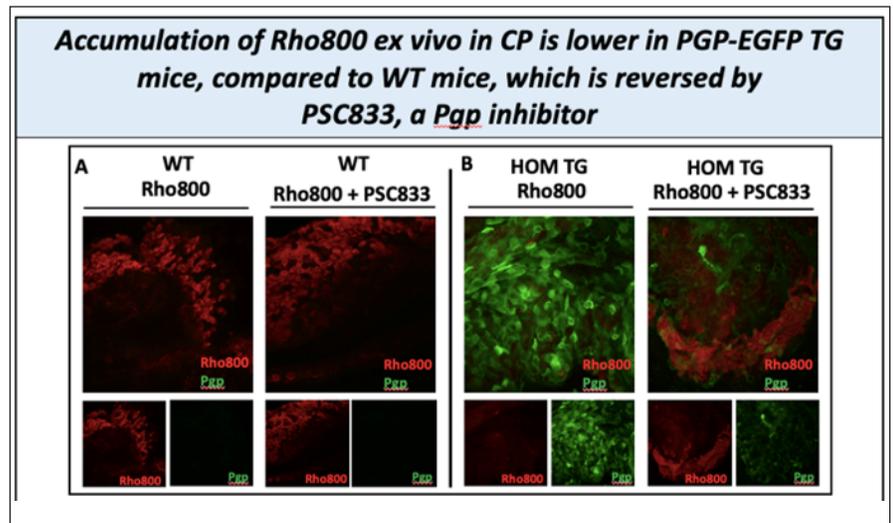
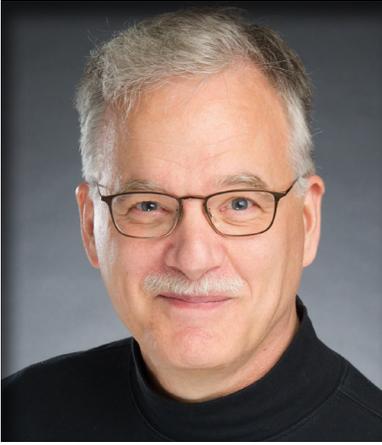


Figure 10. Rhodamine 800 (Rho800) fluorescence, indicating its accumulation, is greater in the CP of (A) WT, compared to (B) CP-PGP-EGFP TG mice, after ex vivo incubation of CP tissues with 5 μ M Rho800 +/- 0.5 μ M PSC833, a specific Pgp inhibitor.



JOHN D. SCHUETZ, PH.D.

Our investigations elucidate how transporters and metabolic pathways impact disease, especially cancer. We have focused on ABC transporters because over a third of the members in this gene family contribute to disease processes. Our recent studies reveal how transporter expression affects the underlying biology of acute myeloid leukemia and medulloblastoma. These findings reveal potential targetable liabilities that we can, through mechanistic studies, leverage to develop novel therapeutic approaches. Thus, our studies provide the basis for targeting transporters in pre-clinical animal models of acute myeloid leukemia and medulloblastoma to improve therapeutic response. One example is shown below.

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, effecting a poor clinical outcome. We discovered that ABCC4 was a candidate driver of SHH-MB. We reasoned that this might account for our finding that ABCC4 overexpression predicts poor overall survival in SHH-MB. Our discoveries formed the basis of elucidating how ABCC4 modulated SHH signaling to impact MB in an animal model. Our studies revealed how suppression of ABCC4 was capable of impairing the activation of the SHH pathway. This knowledge was then applied to a murine SHH-MB model where ABCC4 knockdown significantly reduced tumor burden and extended lifespan (*see Figure 11 below*). 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.

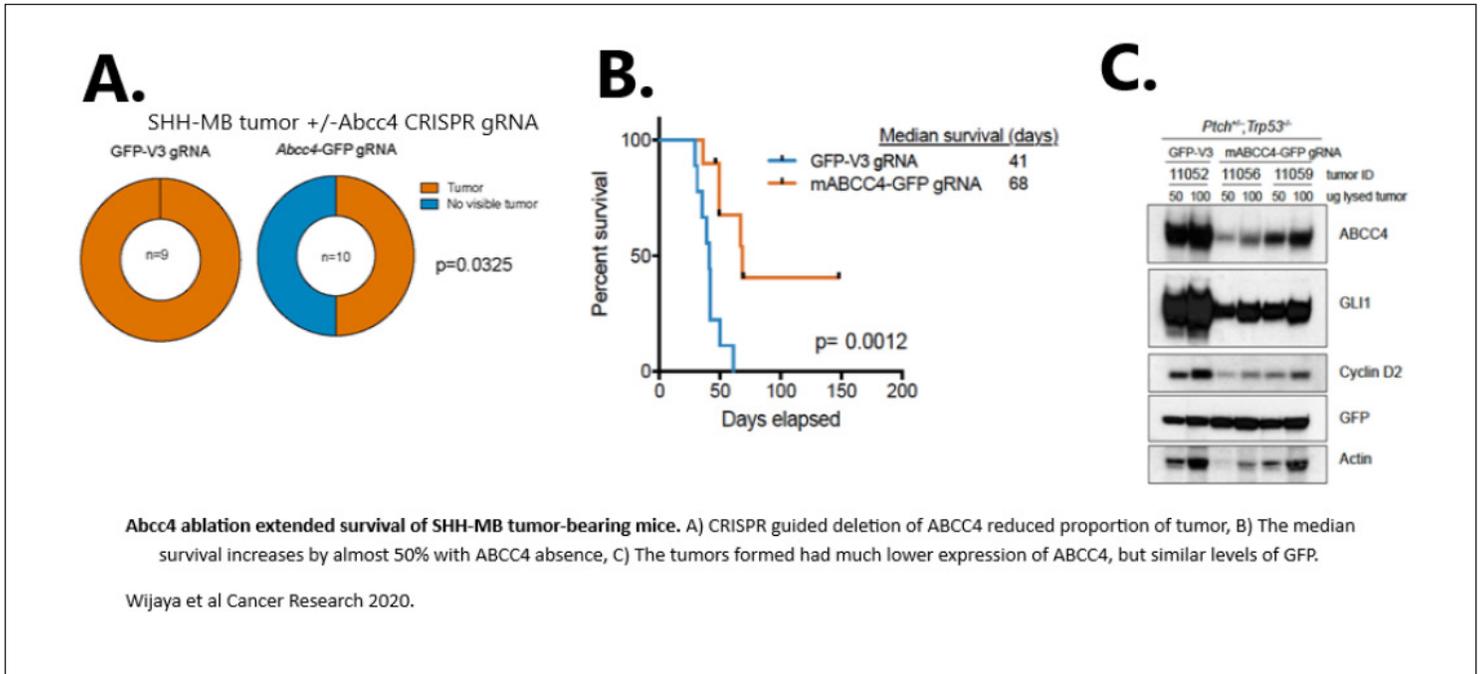


Figure 11.



CLINTON F. STEWART, PHARM.D.

Since joining the Department of Pharmaceutical Sciences in 1991, I have focused my research efforts on developmental therapeutics for children with solid malignancies and central nervous system (CNS) tumors. Clinically, my research involves the application of pharmacokinetic (PK), pharmacogenetic (PG) and pharmacodynamic (PD) approaches to understanding the variability in drug disposition in children with cancer. Little is known about the disposition of anti-cancer agents in infants and young children which could lead to increased risk of morbidity, poor tumor control, and increased incidence of late effects. Thus, we have completed a comprehensive series of pharmacology studies to understand how developmental changes in infants and young children affect the disposition and toxicities of anticancer drugs used in the treatment of infants with malignant brain tumors. For example, we conducted a population pharmacokinetic study of cyclophosphamide and its metabolites in infants with brain tumors.

The results (*see Figure 12 below*) of the covariate analysis revealed the significant influence of patient specific covariates on drug disposition, including patient age as a continuous covariate, phenobarbital cotreatment, and the genotypic variant *CYP2B6* (rs4802101) (*Campagne, Clin Cancer Res, 2020*). By performing these population pharmacokinetic analyses, we can better understand the developmental pharmacology of the drugs used in these infants and achieve our long-term goal to determine rational dosing regimens for infants and young children with CNS tumors.

Our work in the laboratory is guided by addressing clinically relevant problems encountered in the therapy of children with brain tumors, primarily CNS drug penetration of novel compounds used to treat pediatric brain tumors. The preclinical approach we use employs tumor subgroup-specific models of pediatric CNS tumors, cerebral microdialysis sampling of tumor extracellular fluid (TECF) and ventricular CSF, and pharmacokinetic modeling and simulation of the derived data to determine to directly assess the unbound partition coefficient ($K_{p,uu}$) for the drug under study.

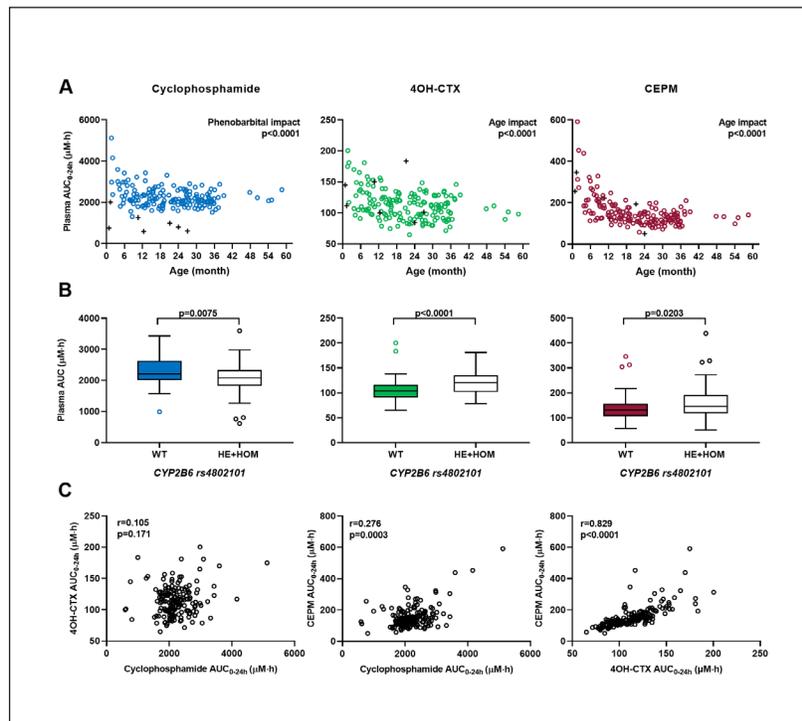


Figure 12. Association of individual cyclophosphamide (CTX), 4OH-CTX, and CEPM exposures with patient covariates. A) Association between CTX, 4OH-CTX, and CEPM AUC_{0–24 h} and patient age or phenobarbital cotreatment. Dots and crosses represent individual drug AUC_{0–24 h} for patients with and without concomitant phenobarbital, respectively. For CTX, the P value indicates the significant effect of phenobarbital cotreatment on drug AUC_{0–24 h} (Wilcoxon–Mann–Whitney). For 4OH-CTX and CEPM, the P values indicate the significant age effect on drug AUC_{0–24 h} (Spearman correlation). B) Boxplots of CTX, 4OH-CTX, and CEPM AUC_{0–24 h} association with the *CYP2B6* (rs4802101) genotype, categorized as WT or variant (HE, heterozygous; HOM, homozygous mutant). P values indicate a significant genotypic effect (Wilcoxon–Mann–Whitney). C) Correlation between individual CTX and 4OH-CTX AUC_{0–24 h}, CTX= and CEPM AUC_{0–24 h}, and 4OH-CTX and CEPM AUC_{0–24 h} values. Spearman correlation coefficients and associated P values are indicated.



JUN J. YANG, PH.D.

I joined the St. Jude faculty in 2010 and I am currently a Member in the Department of Pharmaceutical Sciences, with a joint appointment in Oncology. The research focus of my group is pharmacogenomics of anti-cancer drugs in children, with a particular focus on childhood acute lymphoblastic leukemia (ALL). Relying on a wide range of genomics approaches, our research is aimed to elucidate biological pathways governing efficacy and toxicity of antileukemic drugs, to identify genetic variants associated with pharmacological effects of these agents, and eventually to develop pharmacogenomics-guided treatment individualization for children with these catastrophic diseases.

Because genetic factors in both host and tumor genome can affect drug response, we examine inherited (germline) and acquired (somatic) genetic factors for their association with treatment response in childhood ALL. We have led the first genome-wide association study (GWAS) to identify germline genetic variations associated with minimal residual disease in response to remission

induction therapy in children with ALL (*JAMA* 2009); our work also discovered genetic ancestry-related differences in ALL relapse and leukemia susceptibility (*Nat Genet* 2011 and 2013, *Lancet Oncol* 2015, *Nat Commun* 2015 and 2019).

Applying GWAS to drug toxicity in children with ALL, we have developed a robust research program related to pharmacogenetics of nucleoside analog drugs. We 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 our 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).

More recently, my group has established pharmacotyping platform to directly profile patient leukemia cell drug sensitivity using high-content imaging. Coupling this with systems pharmacology analyses, we identified novel mechanisms for ALL response to tyrosine kinase inhibitors (*Nat Cancer* 2021) and are now developing new ALL therapy using these targeted agents.

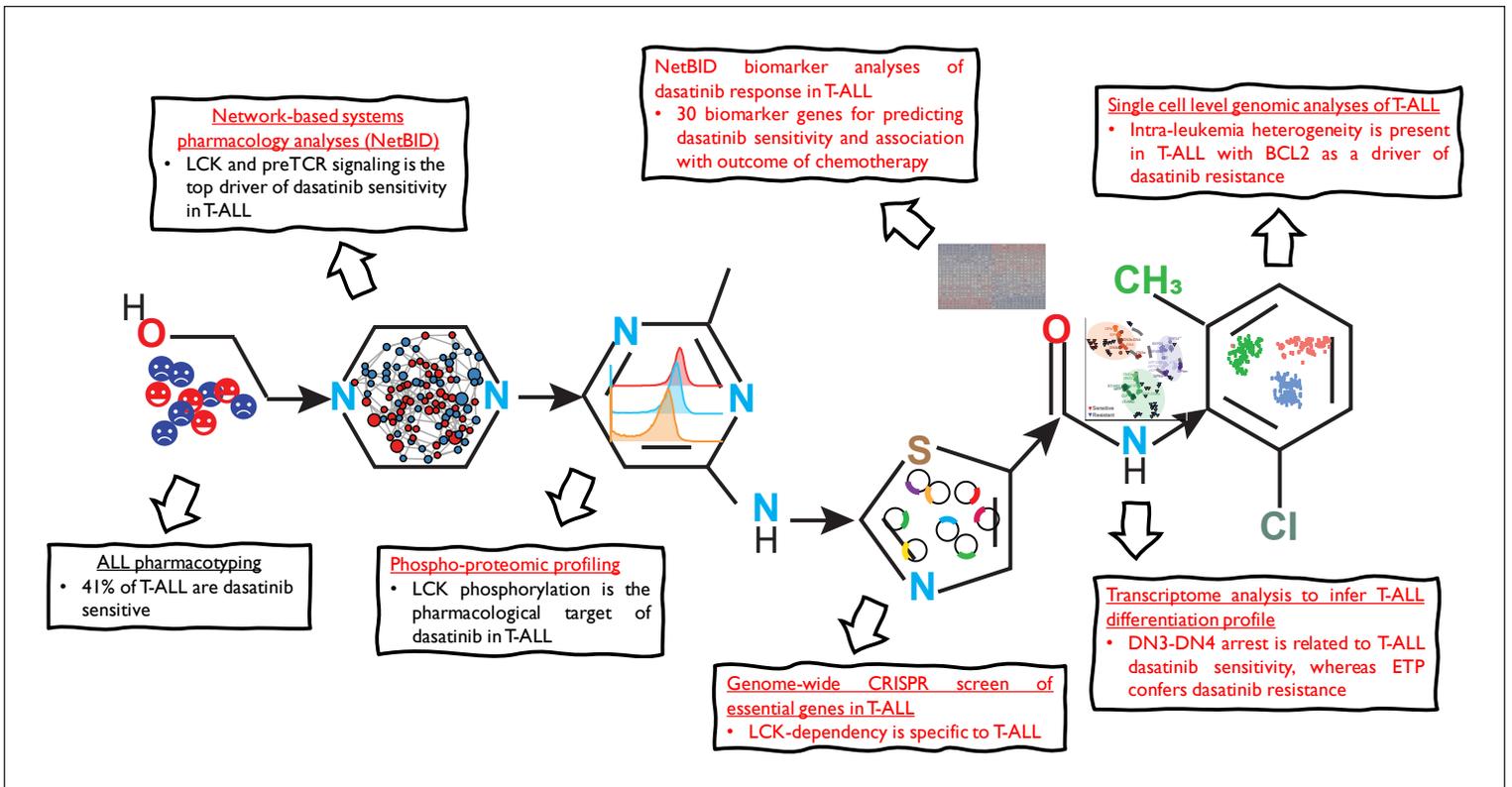


Figure 13.



DANIEL SAVIC, PH.D.

I joined the Department of Pharmaceutical Sciences at St. Jude Children's Research Hospital as an Assistant Member in 2016. I am also a member of the Hematological Malignancies Program at St. Jude, the Pharmacogenomics Research Network (PGRN) and the Center for Precision Medicine in Leukemia (CPML). My primary research focus involves studying gene regulation in the context of childhood acute lymphoblastic leukemia (ALL) in order to better understand genome function and to further define the impact of cis-regulatory elements (e.g. promoters, enhancers, boundary elements) and noncoding sequence variants on chemotherapeutic drug response, chemotherapeutic drug resistance and relapse in childhood ALL. To define the pharmacogenomic role of the noncoding genome, my laboratory utilizes diverse functional genomic and related high-throughput approaches (Savic et al, *Genome Research* 2015, Savic et al, *Genome Medicine* 2016, Ramaker and Savic et al, *Genome Research* 2017) to identify and functionally characterize cis-regulatory elements and their associated noncoding sequence variants.

Our research group is currently working on three related projects that involve: (i) elucidating the role of glucocorticoid response elements (GREs) and other cis-regulatory elements in antileukemic drug resistance (Paugh et al, *Nature Genetics* 2015, Autry et al, *Nature Cancer* 2020), (ii) functionally characterizing noncoding DNA sequence variants implicated in antileukemic drug response, drug resistance and/or ALL relapse, and (iii) developing high-throughput assays to phenotypically screen noncoding sequences *en masse*. Overall, the long-term goal of my research effort is to gain a better understanding of genome function, gene regulation and the genetic factors impacting chemotherapeutic drug response, chemotherapeutic drug resistance and relapse in childhood ALL.

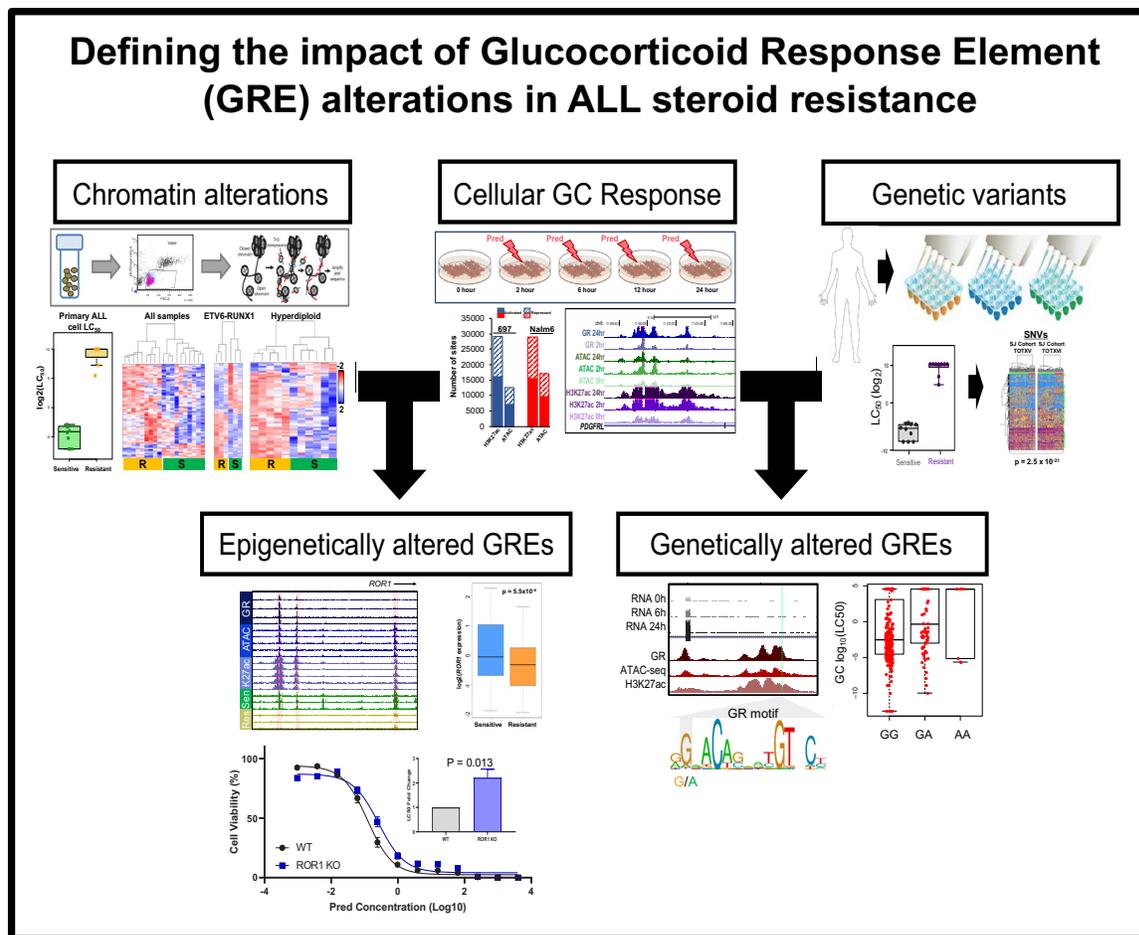


Figure 14.



I joined the Department of Pharmaceutical Sciences as a Research Associate in 2016 and have been an Assistant Member since 2017. I previously studied tissue stem cells in global cancer initiation (Zhu *et al. Nature* 2009; *Cell* 2015; *Cell* 2016). My current research program focuses on elucidating the mechanisms liver cancer metastasis from two different angles: (1) elucidating the function of candidate liver cancer metastasis-promoting genes using 3D cellular models *in vitro* and orthotopic transplantation mouse models *in vivo*; and (2) determine the role of tumor microenvironment (TME) in liver cancer metastasis, particularly the liver TME surrounding tumor mass, the peritumoral TME. We have established unique metastatic liver orthotopic transplantation models using 3D organoids derived from genetic mouse models (Li *et al, Am J Pathol* 2018) and patient-derived xenografts (PDXs). Using these models, we identified a small number of candidate genes that are significantly associated with liver cancer metastasis and are performing functional assays to understand their working mechanisms. We have also found that the secretome of peritumoral hepatic stellate cells induced by tumor-liver interaction is a critical contributor to the dissemination of liver cancer cells. This provides an interesting rationale for targeting tumor-liver secretome as a new therapeutic strategy for liver cancer metastasis. Our work is supported by an ACS and NIH/NCI.

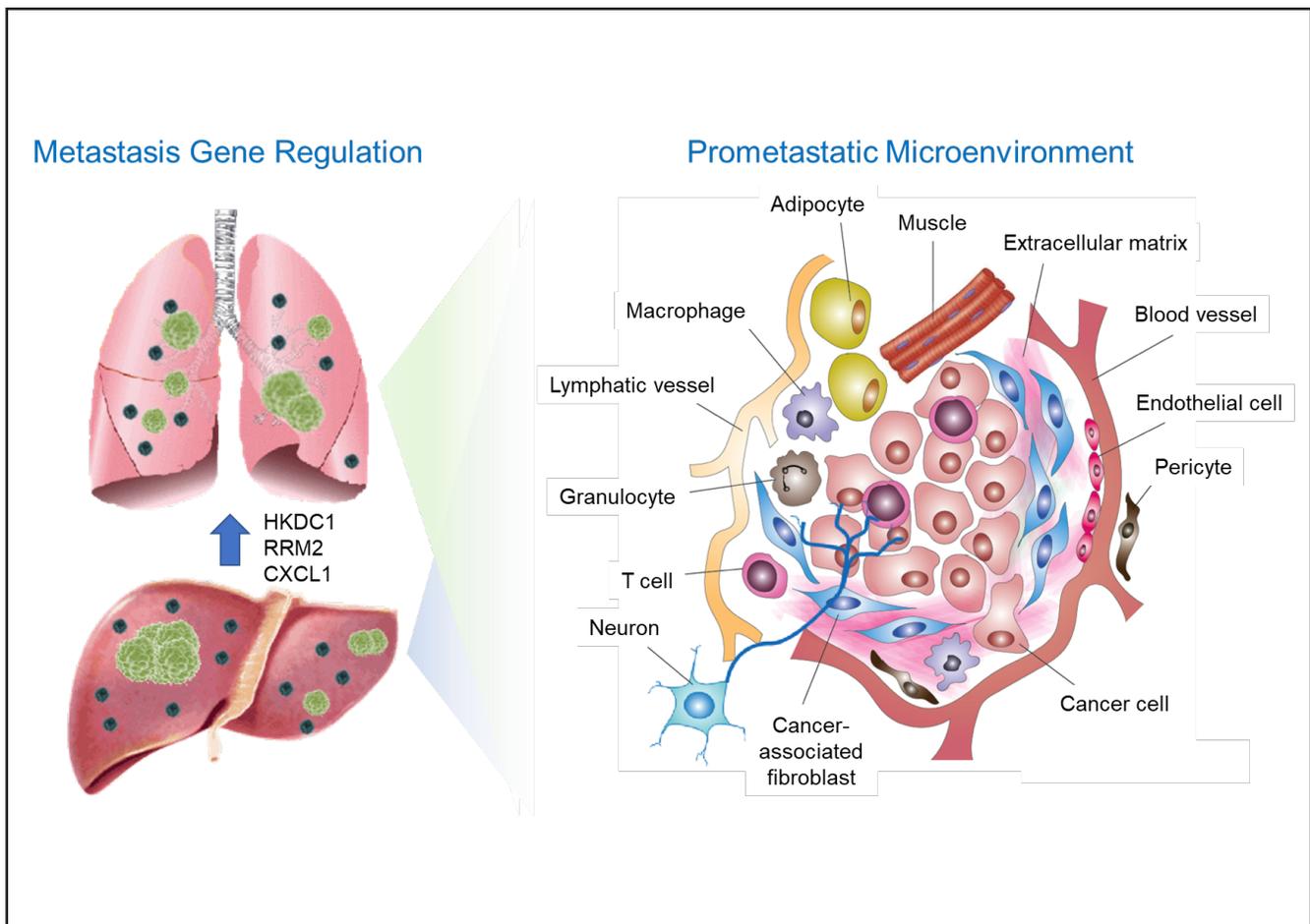


Figure 15.

THE PHARMACOKINETICS SHARED RESOURCE (PKSR)

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



Clinton Stewart, Pharm.D.
Director



Kristine Crews, Pharm.D.

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

4. Develop and apply novel biomedical modeling. Dr. Panetta and the department faculty assist with biomedical modeling, which has three main phases: model design, sampling strategies, and data analysis. The model design phase involves determining the most appropriate pharmacokinetic/pharmacodynamic model which adequately describes the data, considering historical and preliminary clinical data. The sampling strategies phase involves determining the most appropriate sampling times (using D-optimality methods); those that provide the most pharmacokinetic/pharmacodynamic information with the least inconvenience to the patients and staff. The data analysis phase involves determining and using the most appropriate nonlinear curve fitting techniques to best describe the data. These include maximum likelihood estimation, maximum a posteriori probability (MAP) estimation for individual results, and linear and nonlinear mixed effects modeling methods for population results. The biomedical modeling group also supports pre-clinical studies. Examples include the methods developed for quantifying synergy or antagonism in drug combination studies--e.g. Response Surface Modeling for in-vitro studies (**Figure 16** Smith, KH et al. *Mol Cancer Res*. 2020), and tumor growth inhibition modeling for in-vivo studies (Karol S. et al. *PLoS One* 2019).

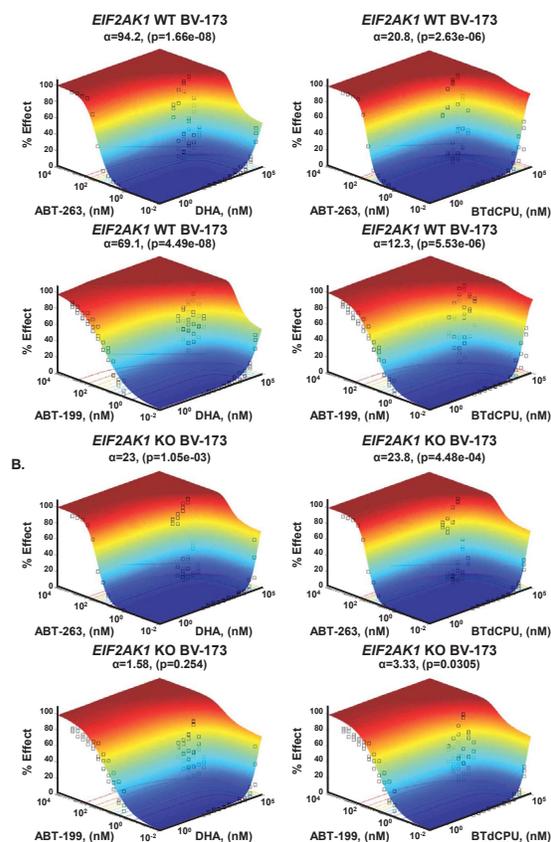


Figure 16. HRI activation synergizes with BH3-mimetics in Ph+ and Ph-like ALL cell lines. Response surface modeling was used to assess synergy in (A) wild-type (WT) or (B) EIF2AK1-KO (HRI-deficient) BV173 cells treated with DHA or BTdCPU combined with ABT-263 or ABT199. The combinations of DHA with ABT-199 or ABT-263 and BTdCPU with ABT-199 were more synergistic in WT cells compared to EIF2AK1-KO cells (the differences in alpha values were significant [$p < 10^{-3}$]).

THE CLINICAL PHARMACOKINETICS (CPK)

LABORATORY

, located in the Department 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}Tc- DTPA. Some of our resources include random access immunochemistry analyzers (e.g. Abbott Architect) and analytical instrumentation (e.g. LC-MS/MS, HPLC).

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

The laboratory staff and pharmacists at St. Jude work closely to provide results in a timely manner. Once a test result is obtained, the laboratory scientists alert the pharmacist, who in turn prepares a clinical consult. This close integration of care assures that our patients receive the best treatment while minimizing adverse 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 as needed.

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



Alejandro Molinelli, Ph.D.
Director, Pharmacokinetics Lab



THE PHARMACOTYPING RESOURCE

located within the Department of Pharmaceutical Sciences supports St. Jude's value of "Embrace the challenge to create a new tomorrow" with the development of a state-of-the-art imaging platform to test drug sensitivity profiles (pharmacotyping) of a variety of pathologic tissues in children with catastrophic diseases, with a focus on pediatric cancer. Directed by Drs. Jun J. Yang and Dr. Kristine Crews, this resource is supported by a team of research technologists with expertise in high-content imaging, drug assay development, preclinical drug evaluation, and research informatics.



Jun J. Yang, Ph.D.



Kristine Crews, Pharm.D.

In the past 40 years, pharmacogenomics has been a central research endeavor of the Department of Pharmaceutical Sciences at St. Jude. Our discoveries of the determinants of drug toxicity and response have fundamentally changed 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 of all pharmacogenomic research. Building upon our historical strength in this field, we recently launched initiatives to modernize our pharmacotyping platforms to better align with rapid advances in cancer therapy and drug screen technologies.

To this end, the Pharmacotyping Resource was established within the Department of Pharmaceutical Sciences in 2020. Currently we are equipped with the 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 without a background in computer programming or coding. It is also equipped with machine learning image analysis capabilities.

Currently, the team is in the process of validating the pharmacotyping assay, which we will first apply to leukemia patients. Every leukemia patient at St. Jude will have his/her leukemia cells tested to at least 40 anti-leukemia drugs within genomic profiling in parallel (whole genome seq, RNA-seq etc.). The integration of these two datasets will drive our pharmacogenomics discovery research and 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 our pharmacogenomics research that will translate to improved cancer treatment outcomes in the future.

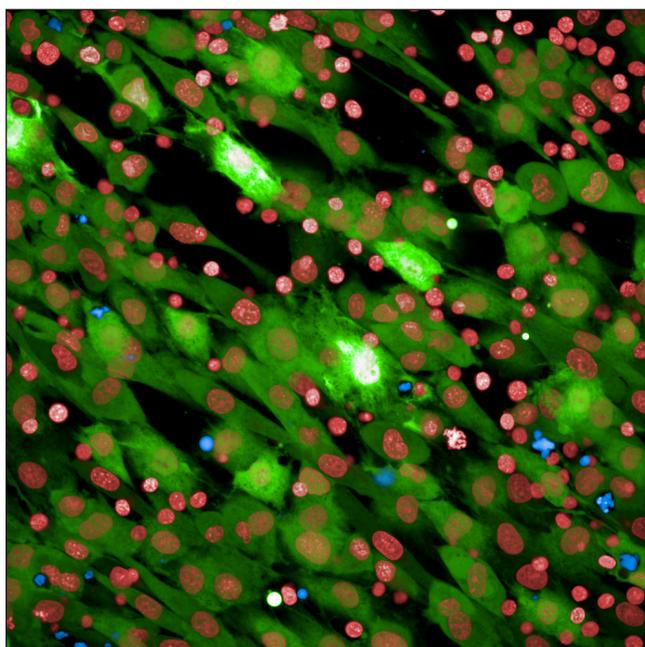


Figure 17. Co-culture of human mesenchymal stem cells (MSCs) that express GFP (green) and acute lymphoblastic leukemia (ALL) cells (RS4;11 cell line). Nuclei are labeled with CyQUANT Red (red) for viable cells and DAPI (blue) for dead cells. Imaged on Operetta CLS with 40X water immersion

PHARMACOGENOMICS RESEARCH

is a particular strength of the Department of Pharmaceutical Sciences, and that has led to clinical implementation of pharmacogenomic tests to benefit St. Jude patients as well as patients worldwide through the department's Clinical Pharmacogenomics Program. The Clinical Pharmacogenomics program has the goal of fully integrating preemptive pharmacogenomic testing into patient care to improve the safety and efficacy of medication use. Toward that end, clinical pharmacogenetic tests for TPMT (Thiopurine S-methyltransferase deficiency) to guide thiopurine use at St. Jude date to the 1990s. In 2011, the multidisciplinary PG4KDS protocol was opened, with a goal to implement pre-emptive pharmacogenetic testing for all actively treated patients at St. Jude. In preparation for this undertaking, and to facilitate evidence-based clinical pharmacogenetic testing worldwide, Dr. Mary Relling co-created the Clinical Pharmacogenetics Implementation Consortium (CPIC®) 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 much involvement from Dr. Cyrine Haidar (SJ Clinical Pharmacogenetics Coordinator), Dr. Kristine Crews (Director, PGY2 Residency in Clinical Pharmacogenomics), Dr. Alejandro Molinelli (Director, PK Clinical Lab), and others. There is direct intersection between CPIC and the Clinical Pharmacogenomics Program, as the eventual goal is to implement all genes and drugs encompassed by CPIC guidelines.

As of 2021, PG4KDS has implemented 13 genes and 66 drugs for over 5500 patients, working closely with Clinical Informatics and clinical departments to create clinical decision support, both pre-test and post-test, to guide rational prescribing. Publications, presentations, and resources are made freely available via the pg4kds website (www.stjude.org/pg4kds). A multidisciplinary Pharmacogenomics Oversight Committee approves

details of all implementations. As each gene/drug pair is approved, the results are placed in the electronic health care records of all past (and future) patients. All tests are performed through the PK Clinical Lab, and are accompanied by consults entered by a clinical pharmacist. Examples of common high-risk drugs whose prescribing is improved include ondansetron, proton pump inhibitors, voriconazole, thiopurines, opiates, and inhaled 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 has become widely recognized as providing a gold standard resource for clinical implementation of pharmacogenomics, and is now incorporated as part of ClinGen <https://clinicalgenome.org/> as the authoritative resource for pharmacogenomic curation.

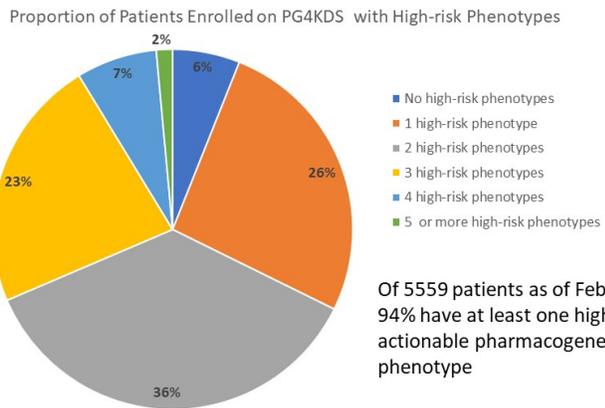


Figure 18.



Kelly Caudle, Pharm.D., Ph.D.



Kristine Crews, Pharm.D.



Cyrine Haidar, Pharm.D.



James Hoffman, Pharm.D., M.S.



Nancy Kornegay



Mary Relling, Pharm.D.

PHARMACEUTICAL SERVICES

is led by Dr. William Greene and is staffed by pharmacists, pharmacy technicians, research and administrative staff, and faculty, (see Organization Chart, page 5) all dedicated to addressing patient care needs as we focus on providing the best pharmaceutical care required for each child at SJCRH 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 different pharmacists are certified as specialists by the Board of Pharmacy Specialties, and four other pharmacists carry credentials 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 noted below.



William Greene, Pharm.D.
Chief Pharmaceutical Officer

Pharmaceutical Services Strategic Plan FY21-22

Mission:

Pharmaceutical Services is a part of the larger Department of 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.

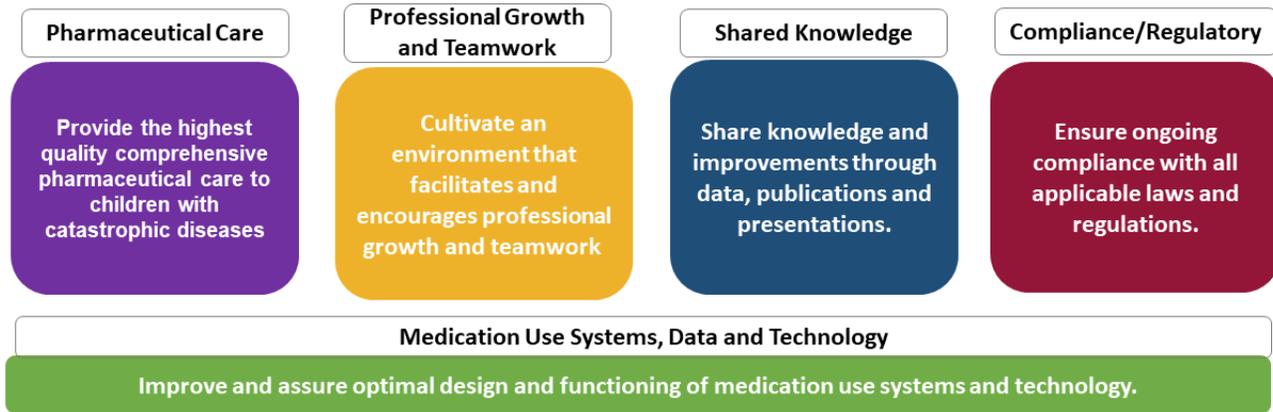


Figure 19.

The 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. PGY2 Pharmacy Residency programs further enhance the culture of learning and growth and help to support academic pursuits and publications.

During 2020, staff from Pharmaceutical Services were co-authors on 25 publications and provided 28 presentations at national/state professional organization meetings.

PHARMACEUTICAL SCIENCES AND THE PANDEMIC

The novel coronavirus SARS-CoV-2 that causes Coronavirus Disease 2019 (COVID-19) brought Pharmaceutical Sciences many challenges. However, we adjusted and our mission and focus continued. We played various roles across St. Jude to respond and continue research and pharmaceutical care. Early in the pandemic, Dr. Bill Evans played an important guiding role in COVID-19 research at St. Jude, which eventually resulted in the St. Jude Tracking Study of Immune Responses Associated with COVID-19 (SJTRC) study. The department has provided significant computational support for the study, and Dr. James Hoffman serves as a co-investigator.

St. Jude created one of the safest harbors against COVID-19 in the nation, and our Department contributed to this effort. Early in the pandemic, it became clear that the virus can also be transmitted by asymptomatic carriers and presymptomatic individuals. St. Jude was one of the first workplaces to develop a comprehensive screening program that included laboratory testing of all employees on campus. All employees working on campus were routinely tested for the SARS-CoV-2 virus 1 or 2 times per week. Upon campus entry, employees are notified if they have been selected for testing. If so, they are directed to an on-site testing facility in the Marlo Thomas Center. The benefits of this program were evident early; affected employees were identified through both the questionnaire and laboratory testing.

James M. Hoffman, Pharm.D., M.S., who is St. Jude's Chief Patient Safety Officer and a Member in Pharmaceutical Sciences collaborated with Aditya H. Gaur, MD, MBBS Medical Director of Occupational Health and Member, Infectious Diseases to develop and administer the comprehensive screening and surveillance program. Dr. Hoffman worked tirelessly with departments and teams across the organization to administer the screening program, including the laboratories involved, human resources, security, and the leadership of the St. Jude Incident Command Center.

As 2020 ended, COVID-19 vaccines brought new promise to help end the pandemic. The infrastructure in the Marlo Thomas Center that Dr. Hoffman helped create was used to provide COVID-19 vaccinations. Dr. Hoffman led the COVID-19 vaccination efforts for St. Jude, and the Department played an essential role in storing, preparing, and providing education for employees as vaccinations started on December 17, 2020.



James Hoffman, Pharm.D., M.S.



Dr. Wendell Cheatham of Pharmaceutical Services bringing the first shipment of the COVID-19 vaccine to the St. Jude campus on December 17, 2020.

PHARMACY CLINICAL DISPENSING OPERATIONS

are led by Dr. William Humphrey (Acute Care; also Pharmacist In Charge) and Dr. Steve Pate (Outpatient Care). 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 Technicians (see Figure below) 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 – preventing unintended consequences of complex therapeutic regimens that may result in either harm or failure to achieve the goal of therapy.



William Humphrey, D.Ph., M.S., M.B.A.
Director, Pharmacy Operations



Steve Pate, D.Ph.
Director, Outpatient Pharmacy Services

These same pharmacists serve as patient and family educators and as resources to our patients and families when drug-related questions arise. Pharmacists also collaborate with Clinical Pharmacy Specialists (see below) to assure proper conduct of medication reconciliation as patients move from inpatient to outpatient care (and back). A team of Clinical Research Pharmacists and 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.

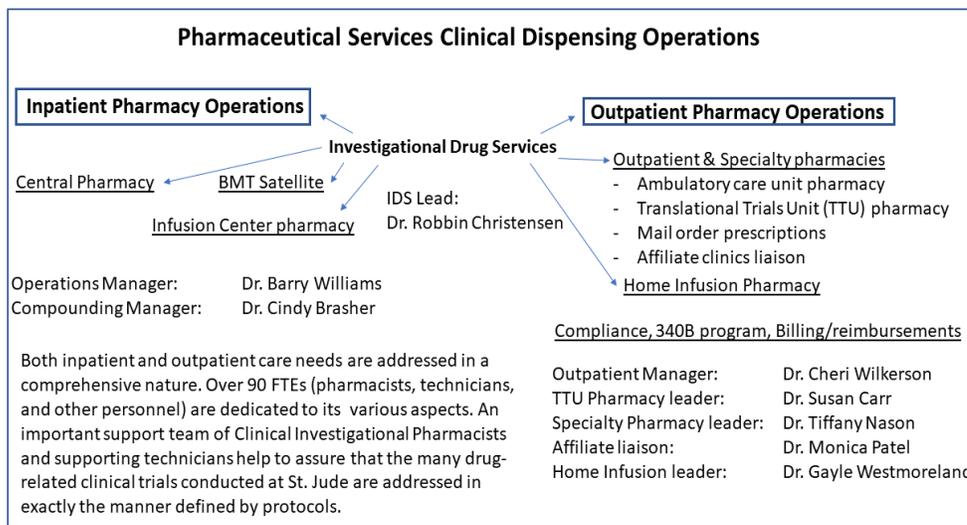


Figure 20.

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.



John McCormick, Pharm.D.,
 Director, Clinical Pharmacy Programs

CLINICAL PHARMACY SERVICES

is led by Dr. John McCormick. Clinical Pharmacy Specialists extend the reach of Pharmaceutical Services directly into the patient care team. (see figure below) Specific teams currently addressed by these clinicians include Leukemia/Lymphoma, Solid Tumor/Neuro-Oncology, Bone Marrow Transplant & Cellular Therapy, Intensive Care, (non-malignant) Hematology, and HIV clinic. These board-certified pharmacists are credentialed members of the medical staff and are given collaborative authority to perform direct patient assessment and prescriber 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 and 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. 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.



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

Unique clinical pharmacy programs focus on Antimicrobial Stewardship (2 dedicated FTEs) and Clinical Pharmacogenomics (see page 21 for more detail). 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. 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. The efforts and impact of Clinical Pharmacy Services reaches globally in the activities and contributions of Dr. Jennifer Pauley, Clinical

Pharmacy Coordinator for Global Pediatric Medicine.

Clinical Pharmacy Specialist Services

Inpatient Care

- Leukemia/lymphoma
- Solid tumor/Neuro-oncology
- BMT & Cellular Therapy
- Non-malignant Hematology
- Intensive Care Unit

Outpatient Care

- Leukemia/lymphoma clinic
- Solid tumor/neurooncology clinic
- BMT & Cellular Therapy clinic
- Non-malignant Hematology clinic

Antimicrobial Stewardship Program

Dr. Shane Cross, Co-Director of Antimicrobial Stewardship



Clinical Pharmacogenomics

Dr. Cyrine Haidar,
 Clinical Coordinator

St. Jude Affiliate Clinics liaison

Dr. P.J. Barker,
 Clinical Coordinator

St. Jude Global

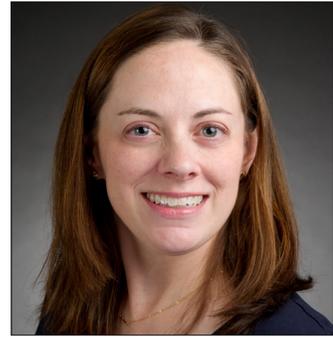
Dr. Jennifer Pauley,
 Clinical Coordinator

Clinical Pharmacy Specialists are integrated into all inpatient and outpatient care teams. These individuals are credentialed within the St. Jude medical staff structure and given authorities and responsibilities for medication therapy plan development, ordering of drug therapy, and related laboratory monitoring and interpretation. All Specialists are Board Certified by the Board of Pharmacy Specialties

Figure 21.

THE PHARMACEUTICAL SERVICES MEDICATION SAFETY AND POLICY TEAM

led by Dr. Jennifer Robertson, is responsible for ensuring safe medication systems throughout St. Jude. The team is finishing their third Medication Safety Strategic Plan and will be developing the fourth iteration in 2021. The current plan focuses on culture of safety, improvement of medication use systems, high-alert medications, and use of technology to improve the safety of medications. 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, and support of ongoing performance improvement related to medication use.



Jennifer Robertson, Pharm.D.
Director, Medication Outcomes & Safety

Many refinements of the system are accomplished each year, impacting physicians, nurses, and pharmacists as they provide patient care.

**St. Jude Children’s Research Hospital
Medication Safety Strategic Plan
FY19-FY20**

Mission:

To improve the medication use systems at St. Jude so that they are safe for every patient every time.

Vision:

To be the premier pediatric institution that is advancing medication safe practices and optimizing medication processes.

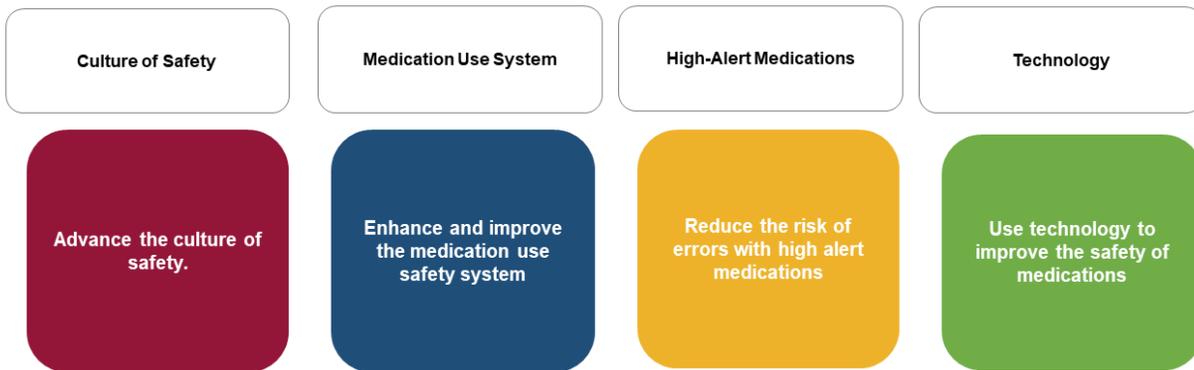


Figure 22.

PHARMACEUTICAL SERVICES INFORMATICS (PSI)

led by Dr. David Aguero, 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, PSI 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 in the Figure below. 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.



David Aguero, Pharm.D.
Director, Medication Systems & Informatics

In addition to this ecosystem, no fewer than 15 different disparate databases and their functionality are maintained by this team. These databases range from inventory control tools to infusion pumps to financial systems and drug information systems and include important trial randomization software.

SJCRH Medication Use Ecosystem Data Exchange (FY21)

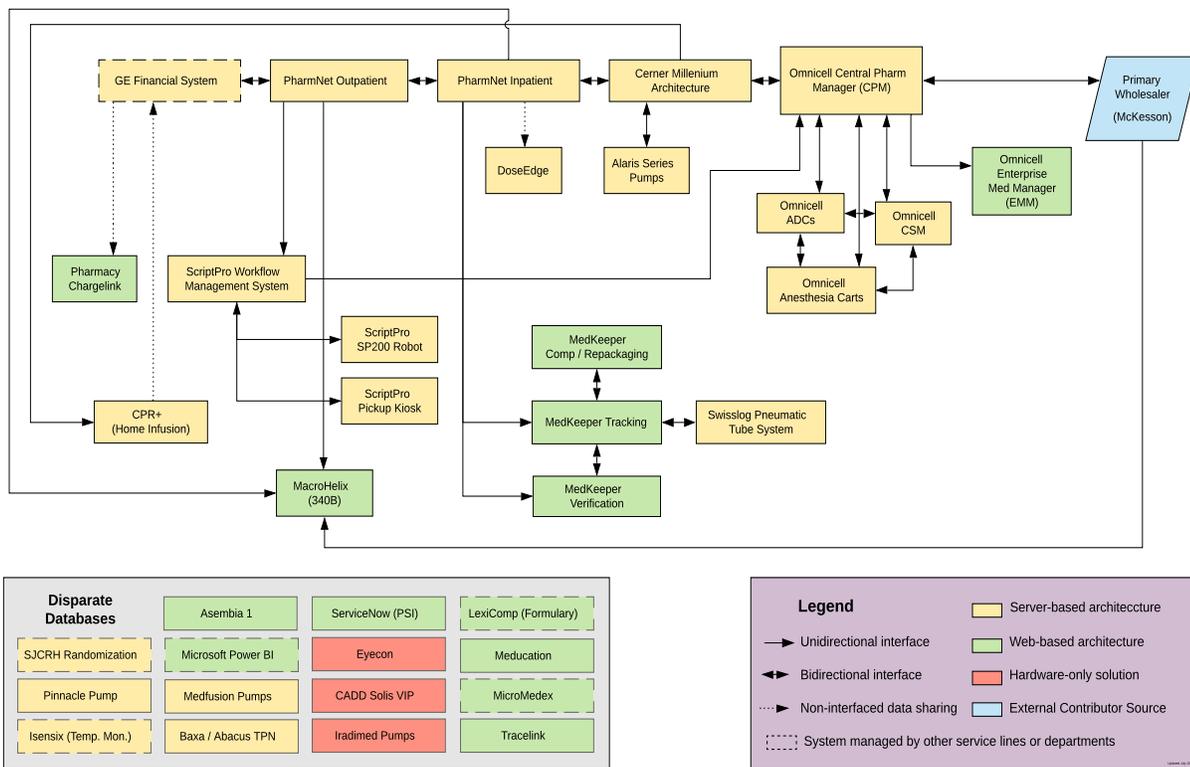


Figure 23.

Finally, PSI Analytics maintains a full data business intelligence portfolio as part of the departmental data strategy. This team assures the access and use of data created during medication management that support and help guide the functions of the department as well as serve as pharmaceutical data stewards within the institution externally.

OUR PGY2 RESIDENCIES IN ONCOLOGY PHARMACY, MEDICATION USE SAFETY AND POLICY, AND CLINICAL PHARMACOGENOMICS

and soon to be Pharmacy 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). Residency programs are expanding in the FY22 fiscal year to include PGY2 training in Pharmacy Informatics (partially supported by a Residency Expansion Grant from the American Society of Health System Pharmacists Foundation). 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 St. Jude's website, www.stjude.org/pharmacyresidency.

St. Jude PGY2 Pharmacy Residents, FY21



St. Jude PGY2 residents 2020-2021: Chelsea Drennan, Pharm.D. (Oncology Pharmacy), Jaclyn Hopp, Pharm.D. (Oncology Pharmacy), Katherine Robinson, Pharm.D. (Pharmacogenomics), and Deann Tims, Pharm.D. (Medication Use Safety and Policy)



HONORS & AWARDS

Congratulations to the **Pharmaceutical Services Clinical Pharmacy Specialists**, who received the **St. Jude 2020 Clinical Care Improvement Award**.

The **St. Jude Antimicrobial Stewardship Program (the AUIC)** was recently recognized as a **Center of Excellence by the Infectious Diseases Society of America (IDSA)** for 2021-2022. St. Jude's stewardship program is coordinated by **Ted Morton, Pharm.D., BCIDP**, and **Shane Cross, Pharm.D., BCPS**, and involves essential collaboration with many clinicians; most notably our clinical pharmacy specialists.

The **Department of Pharmaceutical Sciences at St. Jude Children's Research Hospital** is the recipient of the prestigious **Weaver/Penna Award for 2021** from the **Board of Pharmacy Specialties**. Recipients of this award are recognized for having made outstanding voluntary contributions to the advancement of BPS board certification of pharmacists.

Mary Relling, Pharm.D., received the **2020 ASCPT & FDA William Abrams Lecture Award**.

Delia Carias, Pharm.D., has won the institution's **5100 Award**, one of the highest employee honors at St. Jude.

Mary Relling, Pharm.D., and **Kelly Caudle, Pharm.D., Ph.D.**, are two of nineteen St. Jude scientists and researchers who have been named to the 2020 list of **Highly Cited Researchers**. The list, based on the Web of Science citation index, reflects how often scientists' published research is cited by other investigators, which is a measure of their professional impact.

Katherine Robinson, Pharm.D., has been named to the inaugural class of **Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG) Scholars**. ISCC-PEG is a collaborative group aimed at improving healthcare provider genomics education and is supported by the National Human Genome Research Institute (NHGRI). The Scholars Program provides exposure to the broader genomics community and experts in the field, with the opportunity to work on a genetics/genomics-related education project under the mentorship of an ISCC-PEG member. The appointment is for two years. Katherine will be mentored by Kristine Crews.

Steve Pate, D.Ph., Director, Outpatient Pharmacy Services, and **Barthelemy Diouf, Pharm.D., Ph.D.**, Staff Scientist - Evans Lab, were each featured in this year's **St. Jude Values Book**. Dr. Pate was nominated by Mary Relling, Pharm.D. and Dr. Diouf was nominated by William Evans, Pharm.D. (see

STEVE PATE, D.PH.: PHARMACEUTICAL SERVICES

Discounted drug pricing, third-party reimbursement—these topics usually evoke a yawn. But Steve Pate, D.Ph., knows these details are important. He always keeps in mind the generosity of hard-working donors and the wise stewardship of hospital employees.



Pate seeks reimbursement from third-party payers for dollars spent for medications dispensed to patients. Through the years, he has saved the institution millions of dollars via the hospital's participation in federally sponsored programs and the adoption of best practices from peer institutions. Pate also leads efforts to have St. Jude accredited as a specialty pharmacy, which will save additional dollars.

He's thoughtful about collecting financial information from families, and he often underscores the fact that no patient or family has to pay for care out of pocket.

Pate knows that a dollar saved is a dollar that can be reallocated to another pressing need tied to the hospital's mission of finding cures and saving children.

Nominated by: Mary Relling, Pharm.D., Pharmaceutical Sciences

BARTHELEMY DIOUF, PHARM.D., PH.D.: PHARMACEUTICAL SCIENCES

Dedicated. Innovative. Creative.
Persevering. Fearless.

These hallmark traits define the budding scientific career of Barthelemy Diouf, Pharm.D., Ph.D.



No matter the day or hour, Diouf is most likely at the bench in the Pharmaceutical Sciences lab, working on new research. Beginning at St. Jude as a postdoctoral fellow, his drive led to first-author credits on both basic science and clinical studies published in major journals.

Born in Senegal, educated in France and Germany, and now a citizen of the U.S., Diouf brings a global array of new ideas and strategies to the lab. Fluent in French, English and German, he volunteers his time to help his colleagues in the lab and to collaborate with departments across campus.

His hardworking, methodical approach to research is a shining example of the success of St. Jude—taking unexpected findings and pursuing them to their limits.

Nominated by: William Evans, Pharm.D., Pharmaceutical Sciences

DEPARTMENTAL EXTRAMURAL FUNDING

NEW AWARDS FY2020

Daniel Savic

NIH/NCI R01 - \$2,370,711* - 8/2019-7/2024
Characterizing noncoding GWAS variants in acute lymphoblastic leukemia treatment outcome

Daniel Savic

ACS - \$791,000* - 7/2019-6/2023
Characterizing variants at GWAS loci for acute lymphoblastic leukemia treatment outcome

Clinton Stewart

Pediatric Brain Rumor Foundation- \$70,500* - 1/2020-12/2022
Pharmacokinetic Studies of Trametinib and Everolimus

Jun J. Yang

NIH/NIGMS R41 - \$70,000* - 4/2020-3/2021
Developing high throughput measurement of thiopurine in DNA by mass spectrometry

Jun J. Yang

NIH/NCI R01 - \$799,926* - 4/2020-3/2025
Pathogenesis of ETV6-Related Acute Lymphoblastic Leukemia Yang Component B

*total award amount

OTHER ACTIVE FUNDING FY2020

William Evans

NIH/NCI R01 - \$ 704,703
Pharmacogenomics of Childhood Leukemia ALL

Takaya Moriyama

ALEXS LEMONADE STAND FDN (ALSF) \$50,000
NUDT15 Polymorphisms and Individualization of Thiopurine Therapy in Children with Acute Lymphoblastic Leukemia

Kelly Caudle

NIH/NHGRI U24 - \$981,448
Clinical Pharmacogenetics Implementation Consortium (CPIC)

Mary Relling

NIH/NCI R01 - \$487,994
Glucorticoids in Lymphoblastic Leukemia

Mary Relling

NIH/NIGMS P50 - \$2,918,766
Center for Precision Medicine in Leukemia (CPML)

Mary Relling

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

Mary Relling

Baxalta - \$115,914
Baxalta

John Schuetz

NIH/NCI R01 - \$470,030
Transporters and hematopoietic toxicity

John Schuetz

NIH/NIDDK R01 - \$26,925
Inhibition of Apical cAMP/cGMP transporter (MRP4) in Gut Induces Diarrhea

Clinton Stewart

NIH/NCI UM1 - \$39,986
PBTC-55

Clinton Stewart

Novartis - \$89,874
PBTC-50 CLEE011XUS30T PK

Clinton Stewart

Novartis - \$61,253
Novartis CLEE011XUS39T SJDAWN

Clinton Stewart

Kazia - \$80,462
Kazia GDC-0084 PK Comp SJPI3K

Jun J. Yang

NIH/NIGMS R01 - \$494,399
Genetics-guided Individualization of Thiopurine Therapy

Jun J. Yang

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

Liqin Zhou

AMERICAN CANCER SOCIETY - \$192,250
Molecular and cellular mechanisms of liver cancer metastasis

HIGHLIGHTED PUBLICATIONS

2019 - 2020 PUBLICATIONS

NATURE CANCER

Integrative genomic analyses reveal mechanisms of glucocorticoid resistance in acute lymphoblastic leukemia

Nat Cancer. 2020 Mar;1(3):329-344.

Autry RJ, Paugh SW, Carter R, Shi L, Liu J, Ferguson DC, Lau CE, Bonten EJ, Yang W, McCorkle JR, Beard JA, Panetta JC, Diedrich JD, Crews KR, Pei D, Coke CJ, Natarajan S, Khatamian A, Karol SE, Lopez-Lopez E, Diouf B, Smith C, Gocho Y, Hagiwara K, Roberts KG, Pounds S, Kornblau SM, Stock W, Paietta EM, Litzow MR, Inaba H, Mullighan CG, Jeha S, Pui CH, Cheng C, Savic D, Yu J, Gawad C, Relling MV, Yang JJ, Evans WE

BLOOD

Predicting success of desensitization after pegaspargase allergy

Blood. 2020 Jan 2;135(1):71-75.

Swanson HD, Panetta JC, Barker PJ, Liu Y, Inaba H, Relling MV, Pui CH, Karol SE.

PROC NATL ACAD SCI USA

Massively parallel variant characterization identifies NUDT15 alleles associated with thiopurine toxicity.

2020 Mar 10;117(10):5394-5401.

Suiter CC, Moriyama T, Matreyek KA, Yang W, Scaletti ER, Nishii R, Yang W, Hoshitsuki K, Singh M, Trehan A, Parish C, Smith C, Li L, Bhojwani D, Yuen LYP, Li CK, Li CH, Yang YL, Walker GJ, Goodhand JR, Kennedy NA, Klussmann FA, Bhatia S, Relling MV, Kato M, Hori H, Bhatia P, Ahmad T, Yeoh AEJ, Stenmark P, Fowler DM, Yang JJ.

CLINICAL CANCER RESEARCH

Exposure-Toxicity Association of Cyclophosphamide and Its Metabolites in Infants and Young Children with Primary Brain Tumors: Implications for Dosing.

2020 Apr 1;26(7):1563-1573.

Campagne O, Zhong B, Nair S, Lin T, Huang J, Onar-Thomas A, Robinson G, Gajjar A, Stewart CF.

CANCER RESEARCH

An ABC Transporter Drives Medulloblastoma Pathogenesis by Regulating Sonic Hedgehog Signaling.

2020 Apr 1;80(7):1524-1537.

Wijaya J, Vo BT, Liu J, Xu B, Wu G, Wang Y, Peng J, Zhang J, Janke LJ, Orr BA, Yu J, Roussel MF, Schuetz JD

JOURNAL OF CLINICAL INVESTIGATION

Pharmacogenomics of intracellular methotrexate polyglutamates in patients' leukemia cells in vivo

2020 Dec 1;130(12):6600-6615.

Lopez-Lopez E, Autry RJ, Smith C, Yang W, Paugh SW, Panetta JC, Crews KR, Bonten EJ, Smart B, Pei D, McCorkle JR, Diouf B, Roberts KG, Shi L, Pounds S, Cheng C, Mullighan CG, Pui CH, Relling MV, Evans WE.

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