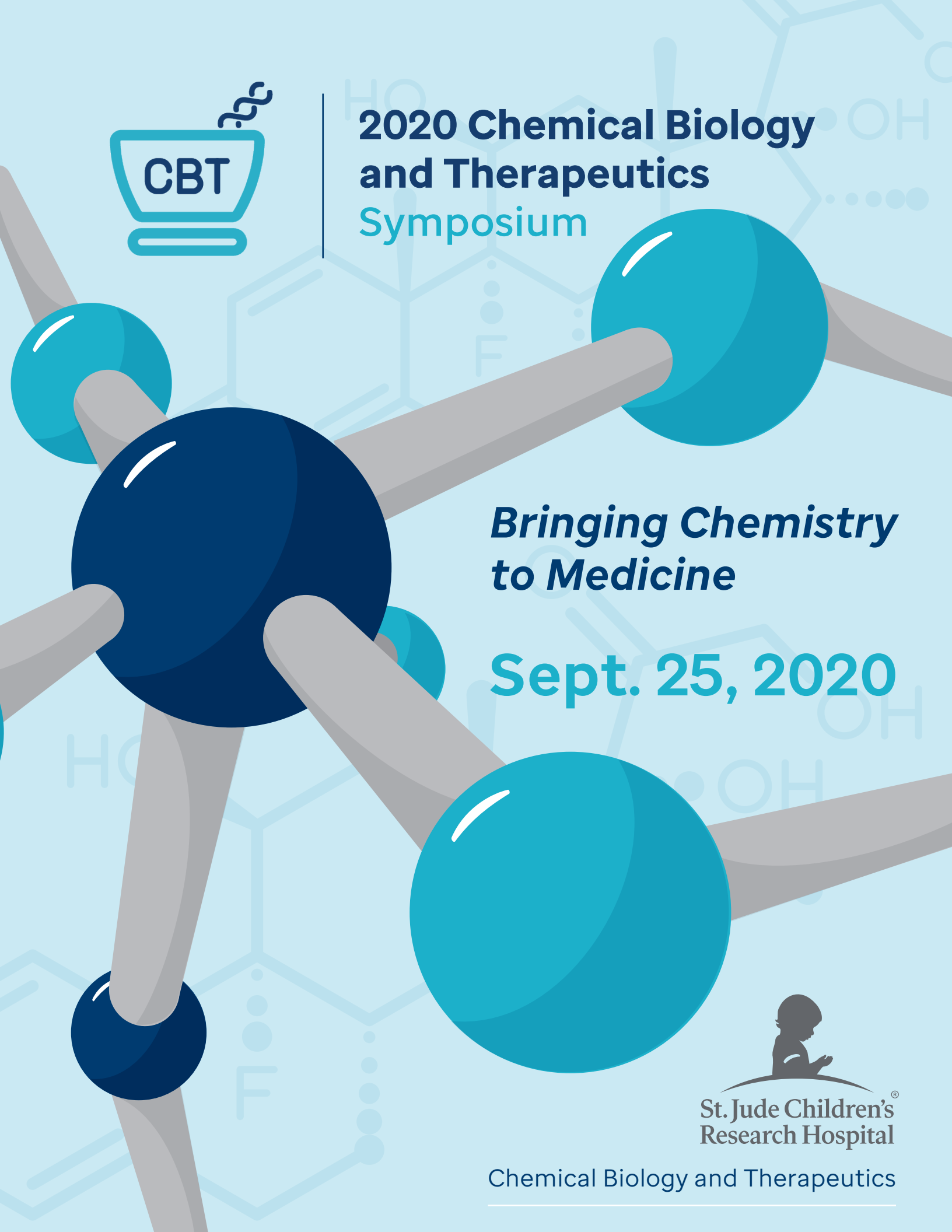
2020 Chemical Biology and Therapeutics Symposium



Bringing Chemistry to Medicine

Sept. 25, 2020

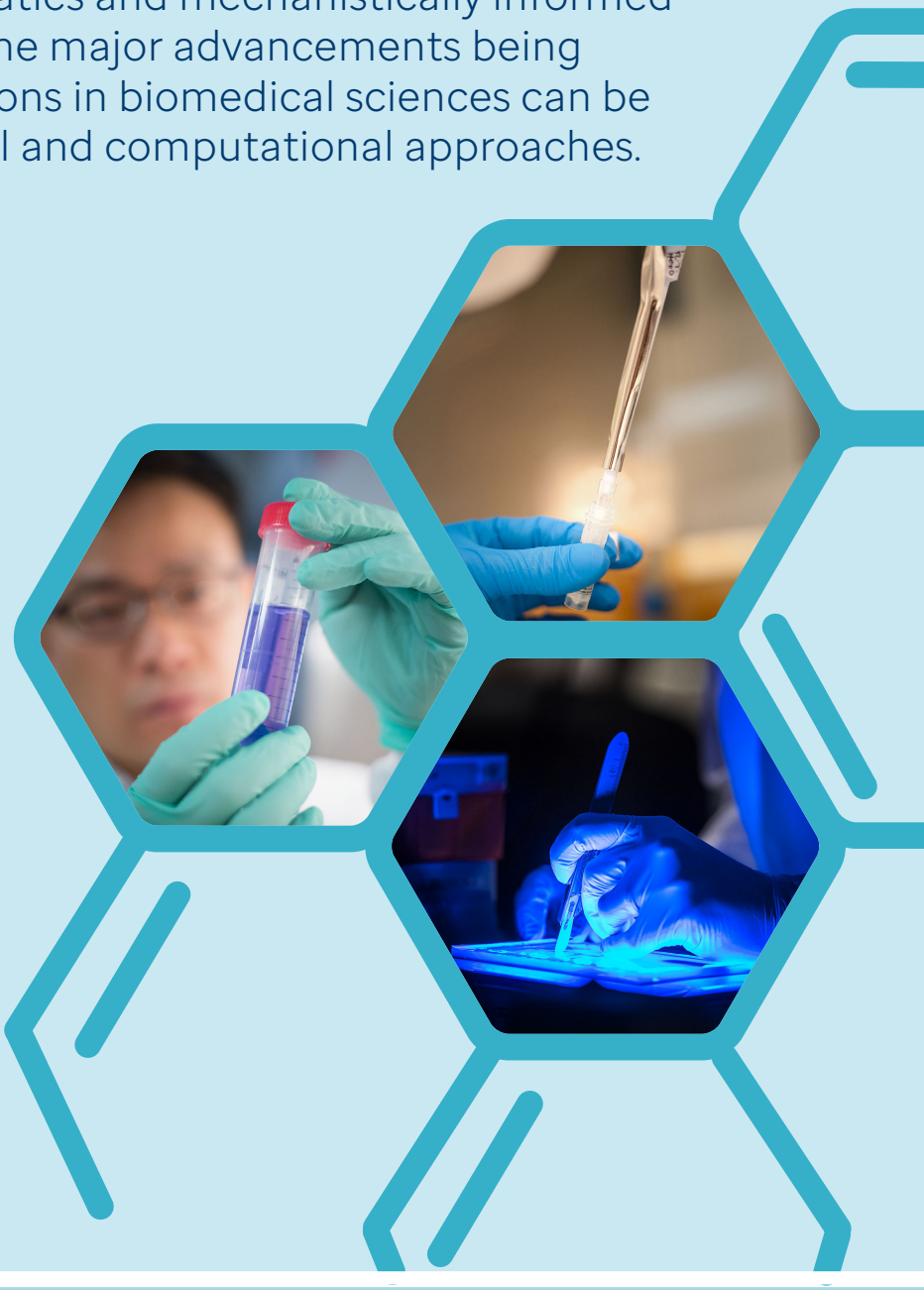
St. Jude Children's Research Hospital®

Chemical Biology and Therapeutics

Chemical Biology & Therapeutics:
Bringing Chemistry to Medicine

Research occurring at the interface of chemistry and biology is discovering and targeting biologic processes beyond gene regulation using cutting-edge and novel chemical approaches. Structure-guided design of smart therapeutics, small-molecule based microarrays, novel chemical library designs, chemical dissection of cell death programs, systems-level chemical informatics and mechanistically informed clinical trials are just some of the major advancements being explored. The emerging questions in biomedical sciences can be uniquely answered by chemical and computational approaches.

The 2020 Chemical Biology and Therapeutics Symposium brings together leading chemical biologists who are pioneering new synthetic approaches to investigate challenging questions in biology and molecular medicine.



Welcome and Opening Remarks

Aseem Z. Ansari

St. Jude Children's Research Hospital

Chair, Chemical Biology & Therapeutics

R. J. Ulrich Endowed Chair

St. Jude and Chemical Biology Research:

The Chemical Biology and Therapeutics (CBT) Department was established to develop innovative chemical and chemoinformatic solutions to fundamental problems in biology and medicine. Present research programs include creation of novel chemical entities that trigger or inhibit gene expression, reveal single molecule and super-resolution imaging of cellular processes, target drug resistance in microbes and humans, and explore protein-ligand dynamics at physiological temperatures. In parallel, the collaborative centers that form the "Therapeutics" component of CBT provide chemical synthesis, high throughput and high content screening, and computational capabilities that match leading biotech/pharma operations and are rarely accessible at academic institutions.

The mission of St. Jude Children's Research Hospital is to advance cures, and means of prevention, for pediatric catastrophic diseases through research and treatment. Consistent with the vision of our founder Danny Thomas, no child is denied treatment based on race, religion or a family's ability to pay.

Julianne Bryan

Master of Ceremonies

St. Jude Children's Research Hospital
Chemical Biology & Therapeutics

Director of Operations
Director of Compound Management
Director of Project Management Office

Julianne Bryan is a pioneer in the application of project management methodologies to scientific discovery environments. She stepped away from bench research and began practicing project management for drug discovery at Scriptgen Pharmaceuticals in 1996. Julie earned a Bachelor of Arts in Biological Sciences from Mount Holyoke College.

Julie moved to Memphis from Boston, in 2005, to create and direct a Project Management Office for lead and probe discovery in the Department of Chemical Biology and Therapeutics (CBT) at St. Jude Children's Research Hospital. She is a certified Project Management Professional (PMP,) Distinguished Toastmaster (DTM,) a charter member of the St. Jude Toastmasters Club, an invited speaker at industry conferences and she leads workshops in the disciplines of project management, communication, and leadership. Julie is the Director for CBT Operations, Compound Management, and the CBT Project Management Office (PMO) at St. Jude.

Outside of work, Julie can be found on the ice, playing and coaching hockey with her three boys, Zack, Kenny and Bryan.

Schedule of Events: Session 1

TIME	EVENT
8:45 - 9:00 am	**Login**
9:00 - 9:15 am	**Aseem Z. Ansari** Welcome and Opening Remarks
Session 1:	
9:20 - 9:35 am	**Scott Blanchard** Bridging the Gap Between Biomolecular Structure and Function Through Single-Molecule Imaging
9:40 - 9:55 am	**Richard Lee** Antibiotic Discovery at St. Jude
10:00 - 10:25 am	**Jun Liu** Painting Chromatin with Synthetic Protein Chemistry
10:30 - 10:40 am	**Break**
10:40 - 11:05 pm	**Angela Koehler** Attenuating Oncogenic Transcription with Small Molecules
11:10 - 11:25 pm	**Taosheng Chen** Chemical Transcription Modulators of Promiscuous Xenobiotic Receptors
11:30 - 11:55 pm	**Shaomeng Wang** Induced Protein Degradation as a Therapeutic Strategy
12:00 - 1:00 pm	**Break**

Schedule of Events: Session 2

TIME	EVENT
Session 2:	
1:00 - 1:15 pm	**Marcus Fischer** Bridge Over Troubled Water Networks – Binding and Garfunkel
1:20 - 1:45 pm	**Ivet Bahar** Network Models in Biology: From Molecular Machinery to Chromosomal Dynamics, to Systems Pharmacology
1:50 - 2:05 pm	**Break**
2:05 - 2:10 pm	**Aseem Z. Ansari** Introduction of Dr. Tommaso Cupido
2:10 - 2:15 pm	**Tommaso Cupido** Introduction of Dr. Tarun Kapoor and Dr. James Chen
2:15 - 2:40 pm	**Tarun Kapoor** Chemical Biology of Drug Resistance
2:45 - 3:10 pm	**James Chen** Targeting Colorectal Cancer with Aldehyde Dehydrogenase Inhibitors
3:15 - 3:30 pm	**Break**
3:30 - 3:45 pm	**Zoran Rankovic** Targeted Protein Degradation Platform
3:50 - 4:15 pm	**Phil Chamberlain** History and Future of Thalidomide Analogs in Human Health
4:20 - 4:55 pm	**Anang Shelat and Phil Potter** Bromodomain-selective BETi as Pediatric Anticancer Agents
5:00 - 5:15 pm	**Tudor Moldoveanu** Probing the Mechanism of Mitochondrial Apoptosis Initiation
5:20 - 5:30 pm	**Aseem Z. Ansari** Closing Remarks

Session 1

Scott Blanchard

9:20 - 9:35 am

Bridging the Gap Between Biomolecular Structure and Function Through Single-Molecule Imaging

Abstract:
The advent of tools enabling the visualization of single molecules has advanced our understanding of the structure-function relationship in biological machines. Such endeavors have contributed meaningfully to a growing appreciation that individual molecules often sample a multitude of structurally distinct native-state conformations during function. To highlight the power of the single-molecule approach, I will summarize our recent work using single-molecule fluorescence resonance energy transfer methods to elucidate the kinetic and structural basis of the ribosome's stepwise movement through the messenger RNA open reading frame. I will also discuss the implications of these findings in the context of identifying inhibitors of the translation mechanism.

About the Speaker:
Scott received his B.S. in Chemistry from the University of California Santa Cruz. He went on to receive a Ph.D. from Stanford University School of Medicine in the Program of Biophysics, where he worked under the direction of Dr. Joseph D. Puglisi. He carried out his post-doctoral research training in the laboratory of Dr. Steven Chu, in Stanford's Dept. of Applied Physics. From 2004-2014, Scott was a tenure-track faculty member in the Department of Physiology and Biophysics at Weill Cornell Medicine (WCM) located within the Tri-Institutional Network that includes Memorial Sloan-Kettering Cancer Center and The Rockefeller University in New York City. Throughout this period, his team strove to develop and implement imaging platforms and data analysis tools to enable single-molecule imaging of complex biological systems. These initiatives have now further extended to include the development and synthesis of "self-healing" organic fluorophores to expand the scope, scale and nature of experimental platforms spanning a range of critical biological systems. Upon his award of tenure in 2014, he served as Associate Director of The Tri-Institutional PhD Program in Chemical Biology. In June of 2019, Scott was appointed Full Member and Endowed Chair of Molecular Imaging in the Department of Structural Biology at St. Jude Children's Research Hospital in Memphis, Tennessee, where his lab continues its efforts to understand the molecular basis of regulation and disease and where he oversees the Center for Single-Molecule Imaging.

Session 1

Richard Lee

9:40 - 9:55 am

Antibiotic Discovery at St. Jude

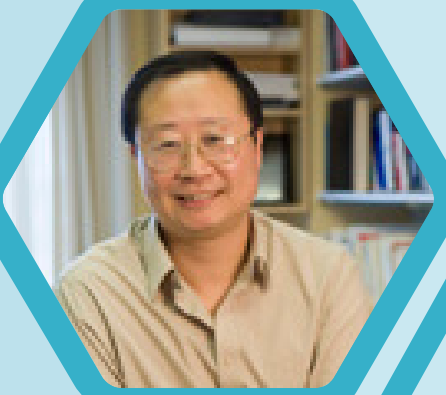
Abstract:
The talk will provide a short overview of the increasing challenge of antimicrobial resistance and how it impacts patient care at St Jude. The problems faced in developing new antibiotics and the strategies that are being applied in the Lee lab to overcome these challenges will also be explored. The generation of next-generation spectinomycin analogs will be highlighted as an example.

About the Speaker:
A native of Manchester, England, Lee received his Ph.D. degree in organic chemistry from the University of Newcastle-upon-Tyne, U.K and subsequently held postdoctoral research fellowship positions at the Department of Microbiology, Colorado State University and Department of Chemistry, Oxford University, UK. He then moved to a research scientist position in the intramural program of the National Institute of Allergy and Infectious Disease, NIH in the laboratory of Dr. Clifton Barry, before taking a tenure-track position at the University of Tennessee Health Science Center, College of Pharmacy. In August 2009 he moved his research program to the Chemical Biology and Therapeutics Department at St Jude Children's Research Hospital. At St Jude his research focuses on anti-infective medicinal chemistry and structure-based drug design, with an emphasis on the design of new inhibitors to treat problematic drug-resistant bacterial infections. Dr. Lee's research has produced several drug candidates including the spectinamide class of anti-tuberculosis antibiotics. He has published over 160 peer-reviewed publications and ten issued patents. His expertise in this area is recognized by frequent service in many government and industrial advisory panels. He is also actively involved in advocacy for the need to develop new antibiotics and how this can be addressed from a chemistry perspective, as highlighted by work with the Pew Charitable Trusts, on the Scientific Priorities for Antibiotic Discovery – Challenges and Opportunities working group and as Co-chair of the 2018 New Antibacterial Drug Discovery and Development Gordon Research Conference.

Session 1

Jun Liu

10:00 - 10:25 am



Rapamycin-Inspired Macrocycles as Novel Chemical Probes and Drug Leads

Abstract:
A major challenge in drug discovery is to identify small molecule inhibitors for the so-called “undruggable” targets that often manifest their activities through protein-protein interactions. Nature has evolved an ingenious solution to this problem as exemplified by the immunophilin ligand family of macrocyclic natural products, including rapamycin and FK506. Aside from their larger sizes that enable more extensive interactions with proteins, these natural products also recruit the FKBP family of intracellular chaperones to form much larger binary complexes before associating with their respective targets, mTOR and calcineurin, blocking the access of substrates to their active sites. Inspired by this unique mode of action, we have designed and generated a 45,000-compound library of rapamycin-like macrocycles, named rapafucins, by fusing the FKBP-binding domain of rapamycin with a combinatorial tetrapeptide library. Screening of the rapafucin library has yielded a number of promising leads that targets a variety of protein targets. Rapafucins are emerging as a new class of novel chemical probes and drug leads.

About the Speaker:
Jun Liu received his BS. in Chemistry from Nanjing University in 1983. He obtained an M.S. degree in organic chemistry from the Ohio State University in 1986 and his Ph.D. in biochemistry from MIT in 1990. After postdoctoral stints at Harvard University and NIH, he returned to MIT to serve on its faculty as an Assistant and then Associate Professor in both the Chemistry and the Biology Departments and the Center for Cancer Research from 1993-2000. In 2001, he became a professor in the Department of Pharmacology and the Department of Neuroscience at the Johns Hopkins School of Medicine. While he was a postdoc at Harvard, he discovered the common target for the widely used immunosuppressive drugs cyclosporin A and FK506 which has had a significant impact in immunology and immunosuppressive drug development. Among his major contributions to drug discovery are the elucidation of molecular mechanisms of action of a number of important natural products including the angiogenesis inhibitor fumagillin, novel inhibitors of eukaryotic translation such as pateamine A and lactimidomycin and the anticancer natural product triptolide. His lab also pioneered the effort on drug repurposing with multiple drugs entering Phase 2 and 3 clinical trials. He has received a number of recognitions including AAAS fellow, Fellow of American Academy of Microbiology and the NIH Director’s Pioneer Award.

Session 1

Angela Koehler

10:40 - 11:05 am

Attenuating Oncogenic Transcription with Small Molecules

Abstract:
Transcription factors that become amplified in cancers are potential targets for therapeutic intervention. A critical path for discovering chemical probes for oncogenic transcription factors will be described along with a vignette related to the discovery of a compound (KI-MS2-008) that binds to the MAX transcription factor that attenuates MYC-driven transcription.

About the Speaker:
Angela Koehler is the Goldblith Career Development Professor in Applied Biology in the Department of Biological Engineering at MIT and an intramural member of the David H. Koch Institute for Integrative Cancer Research at MIT. She is also an Institute Member of the Broad Institute and a Founding Member of the MIT Center for Precision Cancer Medicine. Angela received her B.A. in Biochemistry and Molecular Biology from Reed College in 1997. In 2003, she received her Ph.D. in Chemistry from Harvard University and became an Institute Fellow in the Chemical Biology Program at the Broad Institute and a Group Leader for the NCI Initiative for Chemical Genetics. At MIT, Angela serves at the Faculty Director of the High-Throughput Sciences Facility in the Swanson Biotechnology Center. She is also a co-Director of the MIT Biomedical Engineering Undergraduate Program and a member of the Committee on Pre-Health Advising. Angela has served on the Chemists in Cancer Research Executive Advisory Board for AACR. Awards include being named a Genome Technology Young Investigator and a Broad Institute Merkin Fellow as well as the Novartis Lectureship in Chemistry, the Ono Pharma Breakthrough Science Award, the AACR-Bayer Innovation and Discovery Award and the Junior Bose Award for Excellence in Teaching. Angela serves as a consultant or scientific advisory board member to several pharmaceutical or biotechnology companies and has founded two biotechnology companies.

Session 1

Taosheng Chen

11:10 - 11:25 am

Chemical Transcription Modulators of Promiscuous Xenobiotic Receptors

Abstract:
Pregnane X receptor (PXR) is a xenobiotic nuclear receptor. Many drugs activate PXR to transcriptionally induce drug-metabolizing enzymes and transporters, possibly causing drug toxicity or resistance. The PXR-mediated drug toxicity or resistance can be reversed by knockdown of PXR, suggesting that PXR antagonists have therapeutic value. However, potent and specific PXR antagonist with in vivo activity was lacking, and the ligand promiscuity of PXR has hampered the development of its antagonist. By using chemical biology, structural biology, and pharmacology approaches, we have discovered a potent and selective PXR antagonist with in vivo activity. Unexpectedly, subtle structural modifications of the antagonist, or mutating a single residue within the PXR ligand-binding domain converts the antagonist to an agonist. While ligand binding affinity does not predict PXR's cellular activity, there is a correlation between ligand-induced positioning of the activation function 2 (AF-2) helix and PXR's transcriptional activity. Our studies indicate that it is feasible to chemically control the transcriptional activity of the promiscuous PXR.

About the Speaker:
Taosheng Chen is a Full Member of the Department of Chemical Biology & Therapeutics at St. Jude Children's Research Hospital. He is also the Director of High Throughput Bioscience (HTB) Center at St. Jude. He received his BSc and MS degrees from Fudan University, China, and completed his Ph.D. studies from the University of Vermont, and postdoctoral training from the University of Virginia. Prior to joining St. Jude, Taosheng was a Senior Research Investigator at Bristol-Myers Squibb, and a Research Scientist at SAIC-Frederick, National Cancer Institute. His research laboratory studies the transcriptional regulation of therapeutic responses, by using the promiscuous nuclear receptors (PXR and CAR) as models.

Session 1

Shaomeng Wang

11:30 - 11:55 am

Induced Protein Degradation as a Therapeutic Strategy

Abstract:
In the last few years, induced protein degradation by PROTAC has gained momentum as a new strategy for both targeting validation and therapeutic discovery. In this lecture, I will present our recent research in targeting gene transcriptional factors using the PROTAC strategy. Our data demonstrate that induced degradation of a protein and inhibition of its function by small-molecule inhibitors lead to different outcomes in gene transcription in cells and in cell phenotypes. In addition, our research further demonstrates that induced protein degradation represents a promising therapeutic strategy to target those undruggable or less druggable targets, including transcriptional factors.

About the Speaker:
Shaomeng Wang, Ph.D. has been working on the discovery and development of novel small molecule therapeutics for more than 20 years. Wang received his B.S. in Chemistry from Peking University in 1986 and his Ph.D. from Case Western Reserve University in 1992. His research has focused on targeting protein-protein interactions which regulate apoptosis, including the PPIs between the anti-death Bcl-2 and pro-death Bcl-2 members, the MDM2-p53 PPI, and the PPI of IAP proteins with Smac, which has resulted in the discovery and advancement of 8 compounds into Phase I/II clinical development targeting Bcl-2/Bcl-xL, MDM2 and IAP proteins. In more recent years, Wang has expanded to target a number of PPIs, which regulate epigenetics, including histone readers, writers and erasers. He has also established extensive collaborations with translational scientists and clinical investigators at UMCCC, co-founded five UM start-up companies to help us to bring our drugs into clinical development and marketplace, and published 300+ peer-reviewed papers. Wang was elected as Fellow of the National Academy of Inventors in 2014, the Fellow of the American Association for the Advancement of Science (AAAS) in 2019, and the Hall of Fame of the Division of Medicinal Chemistry of American Chemical Society in 2020.

Session 2

Marcus Fischer

1:00 - 1:15 pm

Bridge Over Troubled Water Networks – Binding and Garfunkel

Abstract:
Solvent organization is a key but underexploited contributor to the thermodynamics of protein–ligand recognition, with implications for ligand discovery, drug resistance, and protein engineering. We explore the substantial contributions of solvent to ligand binding via a single protein mutation without direct ligand contacts. Crystallographic and calorimetric data tack changes in binding affinity due to enthalpically unfavorable perturbations of the solvent network. Water-network changes enable heuristic predictions of the free energy of binding upon changing protein, ligand, or both.

About the Speaker:
Marcus Fischer discovered his passion for structural biology during his undergraduate studies in the beautiful Hanseatic city of Lübeck (Germany). During his B.Sc. & M.Sc. studies he conducted research projects in Montpellier (France), Shanghai (China), and Toronto (Canada). He received a Ph.D. in Structural Biology and Chemistry from the University of York (UK) where he worked with Rod Hubbard on fragment-based ligand discovery. During his postdoc with Brian Shoichet in San Francisco (USA), he traded fog for glacial winter temperatures during a sabbatical year in Toronto. It remains unconfirmed whether the Toronto winter made him question cryogenic practices in crystallography. Marcus joined the faculty at St. Jude Children's Research Hospital in 2017. His lab is exploring protein flexibility and solvation with a view towards using these terms pragmatically in ligand discovery.

Session 2

Ivet Bahar

1:20 - 1:45 pm

Network Models in Biology: From Molecular Machinery to Chromosomal Dynamics, to Systems Pharmacology

Abstract:
One major challenge in computational modeling of protein dynamics is the computational cost and time required for viewing events of biological significance, the time scale and cooperative nature of which is often beyond the reach of conventional molecular dynamics simulations. Elastic network models found wide usage in molecular biophysics and structural biology. More recently, ENMs proved useful to exploring chromosomal dynamics, using data from Hi-C experiments to reconstruct in silico the connectivity of the chromatin and provide physical basis for gene regulation transcription and cell type differentiation. Another topic finding increasingly wider applications is the mapping of the protein-drug interaction space by adopting a bipartite network representation. We will present the foundations of the ENM theory and methods, and new insights gained from the applications to chromosomal dynamics We will further describe recent progress in mapping drugs, proteins and pathways, building on a network-based quantitative systems pharmacology method. We will show how machine learning algorithms that incorporate ENM predictions provide an improved assessment of the effect of mutations on function, compared to those based on sequence and structure exclusively.

About the Speaker:
Ivet Bahar is currently Distinguished Professor and John K Vries Chair at the University of Pittsburgh, School of Medicine, Department of Computational and Systems Biology. Bahar founded the Center for Computational Biology and Bioinformatics in the School of Medicine, which became the Department of Computational Biology in 2004, Department of Computational and Systems Biology in 2010. Additionally, she co-founded in 2005 the first PhD degree-granting program between Carnegie Mellon University and Pitt, which was selected by the HHMI and NIH as one of 10 national programs to provide interdisciplinary research training in biomedical, physical, and computational sciences, and has been continually funded by NIH since then. She was a recipient of the Chancellor's Distinguished Research Award in 2014 and electing to the USA National Academy of Sciences in 2020.

Tommaso Cupido

St. Jude Children's Research Hospital
Chemical Biology and Therapeutics

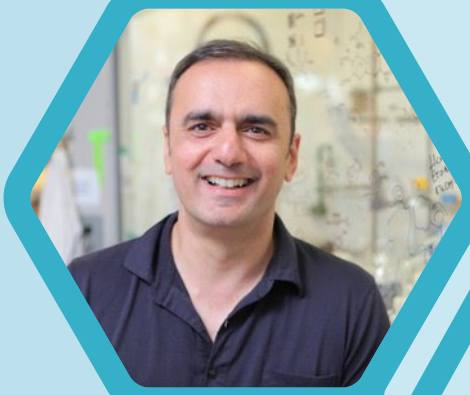
Assistant Faculty Member
Starting November 16, 2020

Tommaso Cupido, Ph.D. is a synthetic chemist who is dedicated to understanding the molecular mechanisms underlying diseases. Cupido received his B.S. and M.Sc. in Biotechnology from the University of Milan (Italy) in 2005 and his Ph.D. in Organic Chemistry from the University of Barcelona (Spain) in 2011. He specialized in chemical synthesis and molecular design of peptides and natural products, developing a keen interest in the chemical bases of biomolecular recognition. He established new methodologies for the synthesis and design under conformational control of naturally occurring peptides and used these synthetic and conceptual advances to improve the potency of a peptide drug in clinical trials. In 2009, he was a visiting fellow at Stanford University in the Department of Chemical and Systems Biology. Since 2012, he has been a postdoctoral researcher at the Rockefeller University in Chemistry and Cell Biology.

Session 2

Tarun Kapoor

2:15 - 2:40 pm



Chemical Biology of Drug Resistance

Abstract:
Characterizing chemotype-specific resistance can help deconvolve a chemical inhibitor's mechanism of action in human cells and achieve 'gold standard' validation of its direct target, i.e. when a silent mutation in the target suppresses drug activity in cell-based and biochemical assays. Examining resistance can help with the use of chemical inhibitors as probes of cellular mechanisms. Phenotypes due to target inhibition can be identified as those observed in wild type cells, across arange of inhibitor concentrations, but not in matched cells with a silent resistant-conferring mutation in the target. Our approach, to design new chemical inhibitors for AAA+ named RADD (Resistance Analysis During Design), involves testing selected chemical scaffolds against constructs with engineered silent mutations. Identifying mutations that confer resistance lead torobust inhibitor-target binding models that guide improvements in inhibitor potency and selectivity.

About the Speaker:
Tarun Kapoor has pioneered the development and use of chemical approaches to decipher cellular mechanisms, focusing on cell division and cancer. Dr. Kapoor graduated from the California Institute of Technology with bachelor's degrees in chemistry and biology (1993). He received both his M.S. (1994) and Ph.D. (1998) in chemistry from Harvard University and did his postdoctoral research at the Harvard Medical School. In 2001 he began his career at The Rockefeller University as an Assistant Professor and Head of the Laboratory of Chemistry and Cell Biology. He was named Associate Professor in 2005 and in 2008 became the Pels Family Professor. In 2012 he also became the Associate Director of The Tri-Institutional Program in Chemical Biology and Program Director of the Cancer Biology Training Grant (T32). In 2016 he was appointed Director of the Pels Family Center for Biochemistry and Structural Biology and Head of the Selma and Lawrence Ruben Laboratory of Chemistry and Cell Biology. He received the 2012 Irving Sigal Young Investigator Award from The Protein Society and the 2008 Scholar Award from the Leukemia and Lymphoma Society. He was an Irma T. Hirschl/Monique Weill-Caulier Trust Scholar from 2004-2009 and a Pew Scholar in the Biomedical Sciences from 2002-2006. Kapoor is an Editorial Board Member of Cell, Cell Chemical Biology, Cell Reports, Developmental Cell and the Journal of Cell Biology. He hasserved on the Review Boards of the Damon Runyon-Rachleff Innovation Award and Pew Biomedical Scholar Award and as an Advisory Board member for the National Institute of General Medical Science of the National Institutes of Health.

Session 2

James Chen

2:45 - 3:10 pm

Targeting Colorectal Cancer with Aldehyde Dehydrogenase Inhibitors

Abstract:
Colorectal cancer is the third most common malignancy, with 1.4 million new cases and 700,000 deaths worldwide each year. Despite preventative screening and surveillance, 20% of colorectal cancer patients have metastatic disease at the time of diagnosis, and 40-50% of early-stage patients will relapse after treatment. Unfortunately standard colorectal cancer therapies are largely ineffectual against late-stage disease, and the 5-year survival rates for these patients is only 12%. Eliminating cancer stem cells (CSCs) could lead to more durable clinical responses, as these self-renewing cells drive tumor relapse, chemoresistance, and metastasis. One promising strategy is the pharmacological targeting of aldehyde dehydrogenase (ALDH) isoforms that promote CSC maintenance, and using CRISPR/Cas9 gene editing, we have confirmed a role for ALDH1B1 in colorectal cancer growth. We have developed first-in-class ALDH1B1-selective antagonists, improved their potency and specificity through medicinal chemistry, and demonstrated their efficacy in colorectal cancer models. We have also solved the crystal structures of ALDH1B1/inhibitor complexes, uncovering the molecular basis of antagonist action and gaining insights for further compound development. Our studies establish a chemical platform for targeting colorectal cancer and other malignancies with ALDH-dependent CSCs.

About the Speaker:
James K. Chen, Ph.D. is the Herbert and Marguerite Jauch Professor and Chair of Chemical and Systems Biology, Professor of Developmental Biology, and Professor of Chemistry at Stanford University. He received his A.B. (1991) and Ph.D. (1998) degrees in Chemistry and Chemical Biology at Harvard University, working with George Whitesides and Stuart Schreiber, respectively. Dr. Chen then studied embryology at the Marine Biological Laboratory (1998) and pursued postdoctoral studies in developmental signaling with Philip Beachy at the Johns Hopkins School of Medicine (1999-2003). Dr. Chen joined the Stanford faculty in 2003, and his laboratory explores the crossroads of organic chemistry, developmental biology, and cancer biology. His current research interests include morphogen signaling, cancer stem cells, spermiogenesis, and optogenetic technologies. He is also the Faculty Director of the Stanford High-Throughput Bioscience Center, and his honors include an NIH Director's Pioneer Award and an NSF INSPIRE Award.

Session 2

Zoran Rankovic

3:30 - 3:45 pm

Targeted Protein Degradation Platform

Abstract:
Targeted Protein Degradation (TPD) is widely seen as a game changing paradigm, which shows promise of having a profound and lasting effect on basic chemical biology research as well as drug discovery. Over the past couple of years the CBT Chemistry Centers developed a TPD platform, which includes PROTAC and Molecular Glues capabilities, to enable effective application of this novel chemical biology approach in research programs at St Jude. This talk will outline the current progress and future directions of this effort, including the development of Phenyl-Glutarimides as alternative cereblon binders for the design of PROTACs with improved chemical stability and degradation efficiency, JAK-PROTACs for the treatment of CRLF2-rearranged acute lymphoblastic leukemia, and identification of potent, selective and orally bioavailable small molecule GSPT1/2 degraders from a focused library of cereblon modulators.

About the Speaker:
Zoran received his Ph.D. in organic chemistry in 1995 from the University of Leeds (UK). That same year he joined Organon (UK), and then continued his medicinal chemistry and drug discovery career within Schering-Plough, Merck, Eli Lilly and most recently St. Jude Children's Research Hospital. Over this period Zoran has been fortunate to be able to contribute to and direct teams that delivered multiple clinical candidates over a range of therapeutic areas including neuro-oncology, neurodegeneration, psychiatry and pain. In the process, he has authored >80 peer-reviewed publications, patents, book chapters and edited two books on drug discovery topics. Since joining St. Jude Zoran's research interests focus on developing small molecule epigenetic modulators and protein degraders for the treatment of pediatric cancers such as medulloblastoma, neuroblastoma, acute lymphoblastic and myeloid leukemia. As the CBT Chemistry Centers director, Zoran's mission is to effectively deploy drug discovery expertise that he gained over twenty years working in pharmaceutical industry and provide state-of-the-art chemistry capabilities to advance research programs at St Jude.

Session 2

Phil Chamberlain

3:50 - 4:15 pm

History and Future of Thalidomide Analogs in Human Health

Abstract:
Targeted protein degradation has seen an incredible amount of interest in recent years, in part due to the immense potential of the degradation technology for drug discovery. The field was rapidly advanced by the discovery that several clinical stage molecules operate via the degradation mechanism. Halidomide was withdrawn from use in the mid-twentieth century after it was found to have caused a tragic epidemic of birth defects. Thalidomide was subsequently found to be useful in treating erythema nodosum leprosum and multiple myeloma, without knowledge of the direct molecular target. Since 2010, a number of discoveries have been made on the molecular basis of thalidomide action. There are now molecular explanations for many aspects of thalidomide biology including the binding tothe cellular receptor, cereblon, the action as a 'molecular glue' degrader for the recruitment of substrate proteins and the molecular basis for thalidomide teratogenicity. In this talk I will review the transformation of thalidomide over the last decade into a well characterized model system for targeted protein degradation by molecular glue.

About the Speaker:
Phil obtained his BA and D.Phil. degrees from the University of Oxford before traveling to the U.S. to work at the Genomics Institute of the Novartis Research Foundation (GNF). At GNF Phil supported and led projects in serious respiratory and inflammatory disease and solved multiple novel structures to support drug discovery efforts. Phil joined Celgene, San Diego in 2007 and built and led the Structural and Chemical Biology department, most recently as Executive Director, Protein Homeostasis and Structural Biology. Phil was responsible for several fundamental scientific breakthroughs on the mechanism of action of thalidomide analogs, including the structural basis for cereblon binding and neosubstrate recruitment, the molecular explanation for species resistance, the definition of the neosubstrate 'structural degron', and a plausible molecular explanation for the thalidomide teratogenicity disaster of the twentieth century. Based on these discoveries, Phil led the construction of the cereblon modulator platform at Celgene, the pioneering drug discovery effort in the 'molecular glue' field. Phil left Celgene/BMS in 2020 to pursue entrepreneurial projects in the targeted protein degradation space. Phil has published work on targeted protein degradation in journals including Nature, Nature Structural and Molecular Biology and Nature Chemical Biology. Phil was the recipient of the John W. Jackson leadership award, the most prestigious achievement award at Celgene.

Session 2

Anang Shelat and Phil Potter

4:20 - 4:55 pm

Bromodomain-selective BETi as Pediatric Anticancer Agents

Abstract:
Inhibition of members of the bromodomain and extra terminal (BET) family of proteins has demonstrated that they are valid targets for cancer chemotherapy. All BETs identified to date contain two bromodomains (BD; BD1 and BD2) that are necessary for recognition of acetylated lysine residues in the N-terminal regions of histones. Chemical matter that targets BET (BETi) also interact via these domains. Molecular and cellular data indicate that BD1 and BD2 have different biological roles depending upon their cellular context, with BD2 particularly associated with cancer. We have therefore pursued the development of BD2-selective molecules, both as chemical probes, and as potential leads for drug development. We will discuss the structure-based generation of a novel series of tetrahydroquinoline analogs that exhibit >50-fold selectivity for BD2 versus BD1. This selective targeting results in engagement with BD-containing proteins in cells, resulting in modulation of MYC proteins and downstream targets. These compounds are potent cytotoxins towards numerous pediatric cancer cell lines and are minimally toxic to non-tumorigenic cells. Additionally, unlike the pan BETi (+)-JQ1, these BD2-selective inhibitors demonstrate no rebound expression effects. Finally, we report a PK optimized, metabolically stable derivative that induced growth delay in a neuroblastoma xenograft model, with minimal toxicity. We conclude that BD2-selective agents are valid candidates for antitumor drug design for pediatric malignancies driven by the MYC oncogene.

Session 2

About the Speaker:
The Shelat lab uses the tools of computational chemistry and chemical biology to investigate the mechanism of drug action and to target disease vulnerabilities, with the goal of translating laboratory findings into human clinical trials. Anang has been instrumental in leading St. Jude's drug re-purposing program for the last ten years, has co-authored over 30 publications related to translational research, and has helped identify new drugs and drug combinations for hematological, solid, and brain tumors. Anang graduated from Harvard University with a B.A. in Biochemical Sciences and completed his PhD under the mentorship of Drs. Kip Guy and Tack Kuntz in the Department of Chemistry

About the Speaker:
Dr. Potter received his PhD from the University of Manchester, UK, studying chemical carcinogenesis and DNA repair. Following a postdoctoral fellowship at the Paterson Institute, he moved to St. Jude Children's Research Hospital and was promoted to the faculty in the Department of Molecular Pharmacology. In 2010, he joined Chemical Biology and Therapeutics.

The Potter lab has sought to generate novel approaches for the treatment of pediatric solid tumors by selectivity modulating drug activity in vivo. This has been accomplished using the specific delivery of carboxylesterases to metastatic lesions in mice bearing disseminated neuroblastoma. Following treatment with irinotecan, tumor regressions are observed, leading to long-term survival of the animals. Clinical trials for this technology are currently underway. Recently, work has focused on the development of novel bromodomain-specific inhibitors targeting pediatric tumors. These studies, conducted in collaboration with Shelat group, will be discussed at the upcoming symposium.

Session 2

Tudor Moldoveanu

5:00 - 5:15 pm

Probing the Mechanism of Mitochondrial Apoptosis Initiation

Abstract:
Mitochondrial apoptosis is orchestrated by the BCL-2 family proteins, which regulate the integrity of the mitochondrial outer membrane. Mitochondrial poration is a key initiating event in apoptosis mediated by the pore-forming BCL-2 proteins BAK and BAX. The regulation of these proteins is remarkable, and I will present an overview of our current understanding of this process touching on the mechanism and probing of BAK activation.

About the Speaker:
Moldoveanu lab research centers on structural and chemical biology of apoptotic and necroptotic programmed cell death. Tudor received his BS and PhD in Biochemistry from Queen's University in Canada, training in the protein biochemistry and structural biology of calcium-dependent calpain cysteine proteases with Dr. Peter Davies. As a postdoc, Tudor trained on the structural biology of apoptotic BCL-2 proteins with Dr. Kalle Gehring at McGill University in Canada as a Canadian Institute of Health Research postdoctoral fellow, and subsequently trained more broadly on the biology of programmed cell death with Dr. Doug Green at St. Jude Children's Research Hospital.

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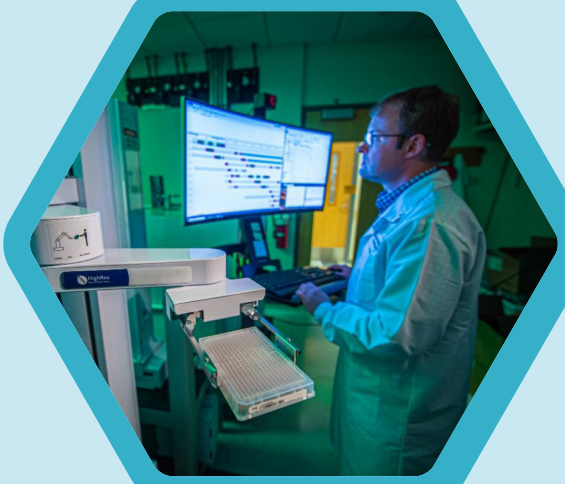
Chemical Biology and Therapeutics

The Chemical Biology and Therapeutics Department at St. Jude was established to develop innovative chemical and chemoinformatic solutions to fundamental problems in biology and medicine. Present research programs include creation of novel chemical entities that trigger or inhibit gene expression, reveal single molecule and super-resolution imaging of cellular processes, target drug resistance in microbes and humans, and explore protein-ligand dynamics at physiological temperatures. In parallel, the collaborative centers that form the “Therapeutics” component of CBT provide chemical synthesis, high throughput and high content screening, and computational capabilities that match leading biotech/pharma operations and are rarely accessible at academic institutions.



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