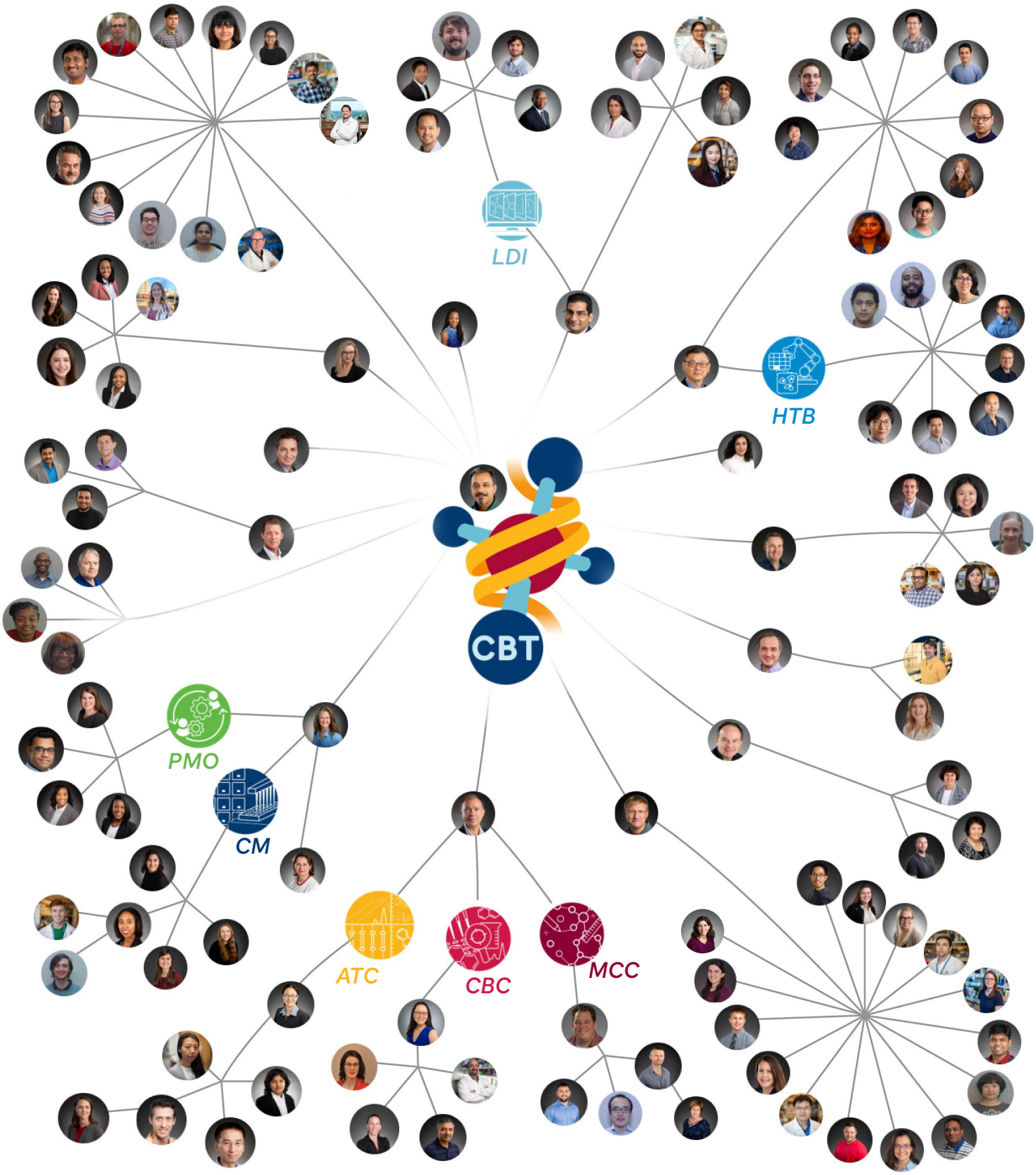
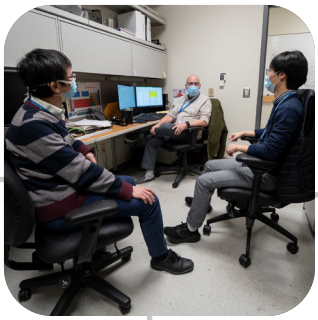
THE CBT CATALYST

Finding cures.
Saving children.





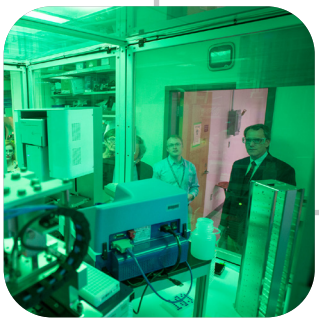













What's New, CBT?

The distinction between Chemical Biology and its siblings (biochemistry, biological chemistry, and of course bio-organic chemistry), lies in the unabashed use of chemical approaches to gain insights into biology and dysfunctional processes that cause disease. This young and vibrant discipline adds the power of chemistry to the rich palette of biological, physical, and computational tools that are typically used to reveal the intricacies of cellular function and dysfunction. When, in this curiosity-driven pursuit, new chemical matter is found or created to target disease vulnerabilities, it inherently opens a path to finding cures for ailments that might have evaded prior interventions.

As manifest in the name, our discipline bridges chemistry and biology, and as such it thrives on collaboration and cross-pollination between the practitioners of its two progenitor disciplines. It is this spirit of collaboration that we highlight in three acts of this issue of the **CBT Catalyst**. The first section focuses on CBT's seven Collaborative Centers that seamlessly integrate "pharma-scale" capabilities to identify and develop small molecules as leads for therapeutics. Rather than functioning as a turn-key operation, center members engage in thoughtful pre-consultations with biomedical colleagues to develop solutions for seemingly intractable problems. The intermediate section shines light on CBT's multifaceted outreach beyond our department to colleagues at St. Jude and across the world. The final section celebrates the innovative science being conducted by members of the CBT community. We invite you to join us in our mission to discover, innovate, find cures and save lives.

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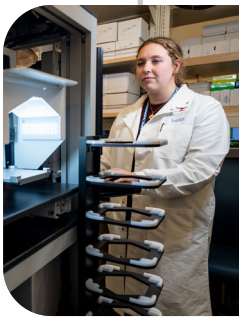
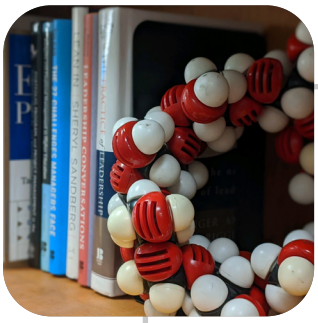
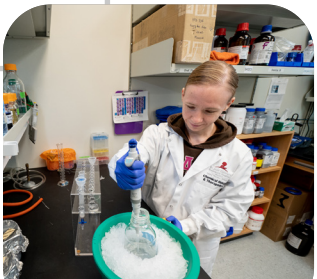
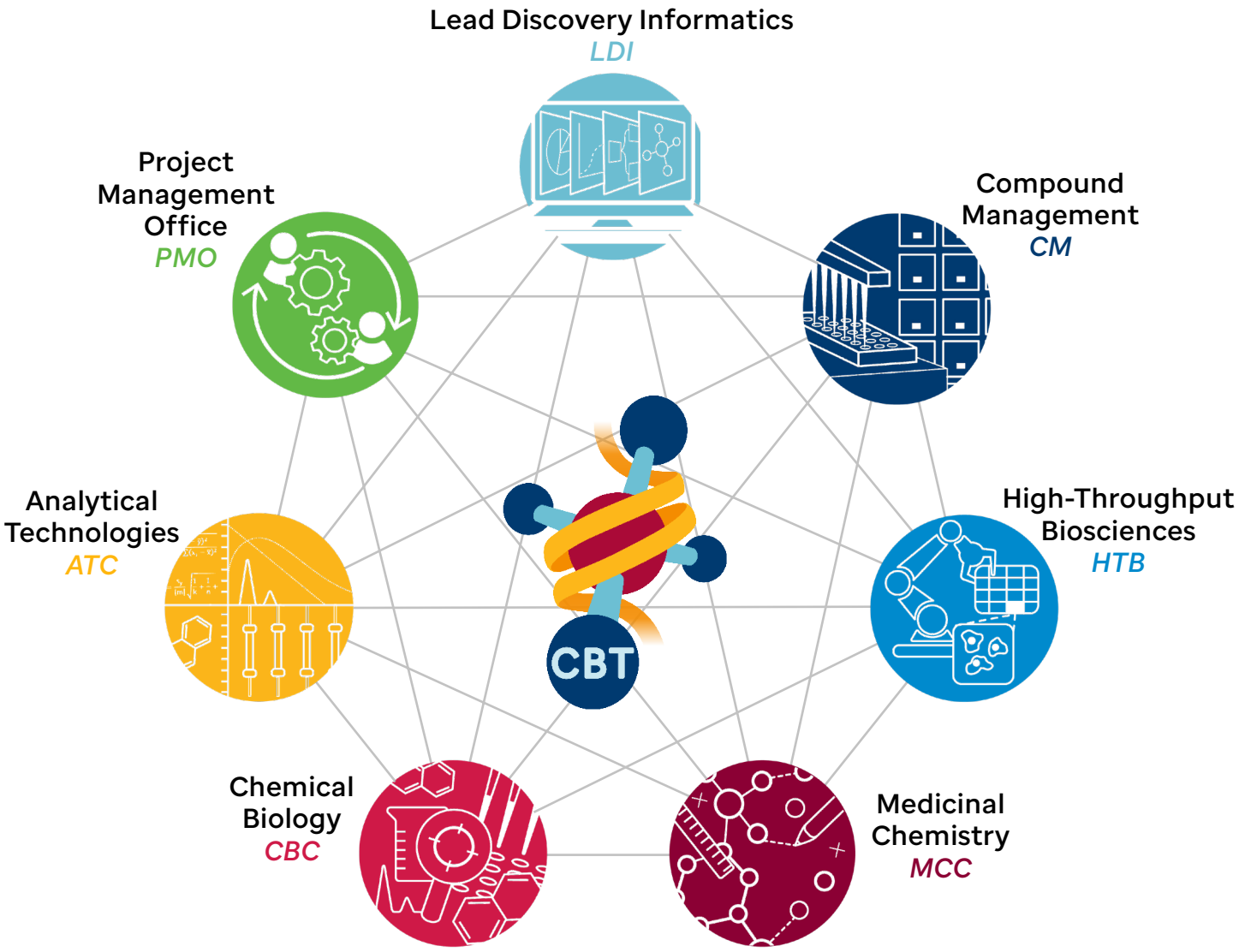




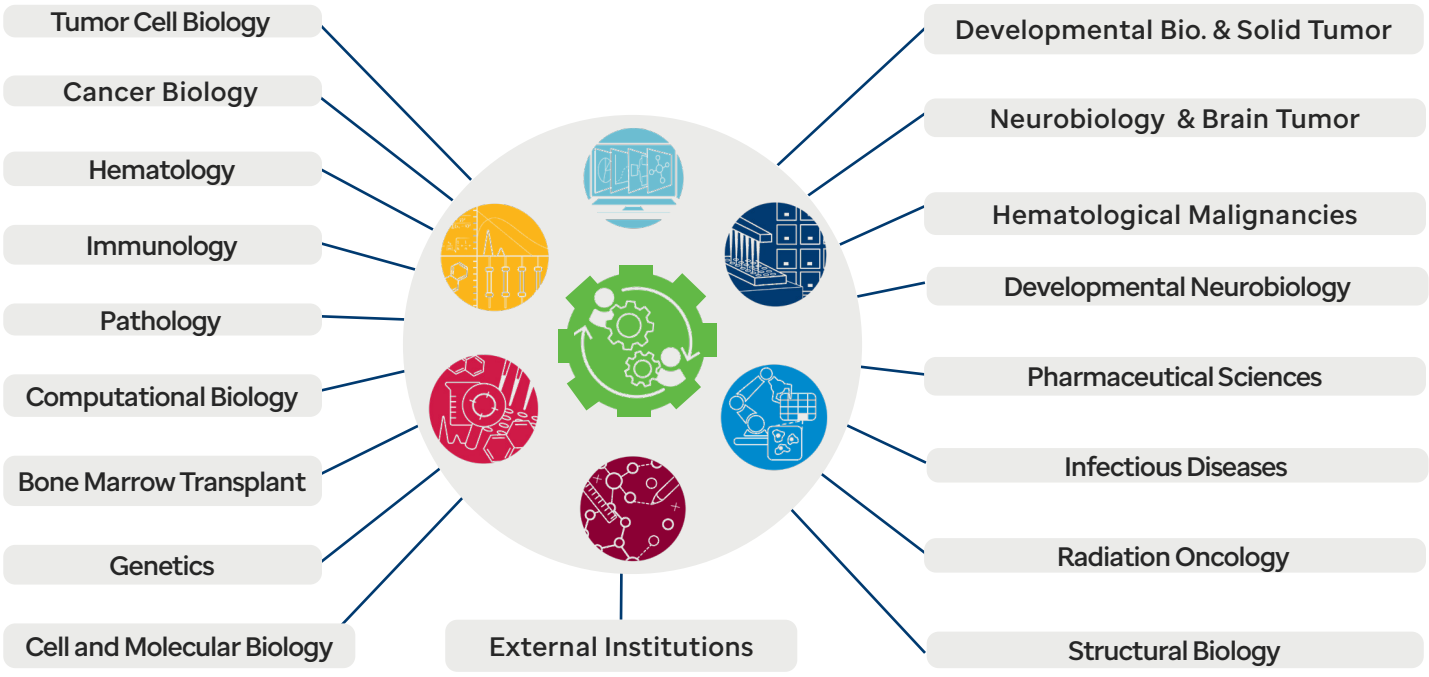




CBT Collaborative Centers

Leading state-of-the-art chemistry technologies centers focus on collaborative research with St. Jude investigators to further our understanding of biological mechanisms that result in childhood diseases. The overarching goal is to translate this knowledge into new therapeutic opportunities. **CBT centers** form an integrated pipeline to bring chemistry to medicine at St. Jude. Collaborative projects involve a close partnership between the laboratory and the participating centers.

Unlike shared resource centers, we are, by design, a collaborative department that develops innovative chemical and chemoinformatic solutions to tackle fundamental problems in biology and medicine. The collaborative centers possess chemical synthesis, high-throughput and high-content screening, analytical, pre-clinical, and computational capabilities that mirror leading biotech/pharma operations and are rarely accessible at academic institutions.



A Future of Collaboration

How we currently collaborate

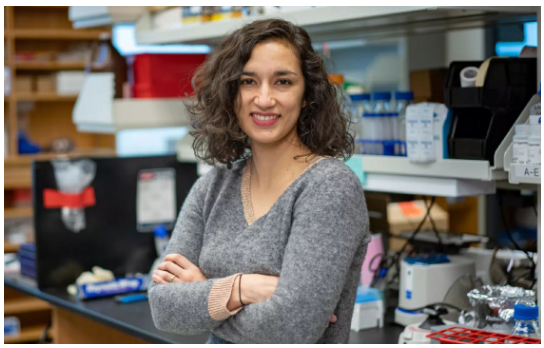
The Therapeutic Resource Allocation Committee (TRAC) advises and helps CBT allocate its resources to a portfolio of St. Jude projects.

Steps to Initiate Collaborations

We are actively growing our collaborative network across St. Jude and invite you to join us.

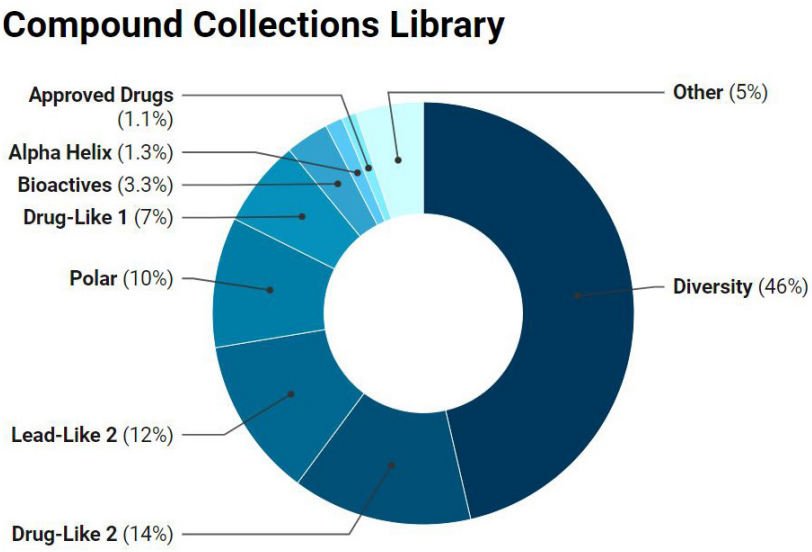
1. **Contact Us**
   Present at the weekly *CBT seminar series*, interactive *CyberTea* presentations, and/or informal *Outside the Box* discussions.
2. **Pre-consultation**
   Interactive meetings where the investigator, CBT collaborative center directors and CBT faculty share their expertise and collectively discuss the scientific and/or translational goals and develop a path for effective collaboration.
3. **Develop Approaches**
   Together we develop meaningful chemistry-based approaches to interrogate pathways and address key biological questions related to the investigator's proposal.
4. **Partnership**
   In partnership with the investigator, we seek to translate outcomes of these collaborations (chemical discoveries) into new therapeutic opportunities.
5. **TRAC (Therapeutics Resource Allocation Committee)**
   An excellent opportunity for principal investigators at St. Jude to access resources for their research goals and benefit from the collective knowledge and expertise of the CBT collaborative centers.

To learn more, contact: **Carolina Adura**
carolina.adura@stjude.org



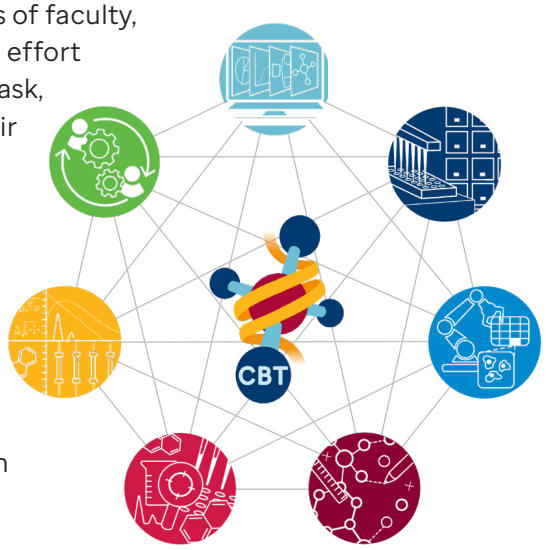
Centers in Action: A CBT Library

With one of the largest compound collections in academia, containing over 600,000 carefully annotated small molecules, CBT is paving the way in drug-discovery research. With a screening library of this complexity, it's no surprise CBT has a curated team of scientists who maintain and enhance it behind the scenes. **Gisele Nishiguchi**, leader of the compound collections team and principal chemist in the Chemical Biology Center, came to St. Jude three years ago after spending over 12 years in industry doing lead optimization and clinical candidate selection. "Industry is a scientifically exciting, high-pressure environment with a lot of responsibilities," explains Gisele. "I was looking for a transition to something that would be more focused on the science and the patients. I had always been attracted to the cutting-edge research of academic institutions and the mission-focused and strong commitment of non-profit organizations." In the position originally conceived by Zoran Rankovic and Richard Lee, Gisele now leads a team of 4 scientists from multiple different CBT centers who curate the collection. The team includes **Jason Ochoada** (LDI), **Sourav Das** (LDI), **Shalandus Garrett** (ATC & CM), and **Duane Currier** (HTB). "What makes us unique is having a team to manage all of it. We have medicinal chemists, computational chemists, and automation experts, which enhances our ability to collaborate."



In the beginning, the team's main goal was to assess the contents of the collection. Currently, it contains small molecules from vendors, compounds from in-house parallel synthesis, analogs of internal medicinal clinical candidate projects, focused libraries designed for specific targets or target classes, fragments, natural products, approved drugs, and chemical probes from literature. It is organized in a 'library of libraries' design, where subsets can be screened independently according to a project's specific needs. When asked about the goals of the compound collections team, Gisele mentioned modernization. "We want to support relevant, modern research because science is always evolving. Targets have changed, compounds have changed, and we wanted to upgrade the collection constantly."

The team's objectives are to leverage and expand the existing library by acquiring compounds enriched for biological activity and new approved drugs and probes. The team meets every two weeks to keep up with maintenance and discuss project collaborations. "Our initial goal is really to support the needs of faculty, whether inside or outside the CBT fold," mentions Gisele. "We put a lot of effort into reaching out to them, so they can let us know what they need. We ask, 'do they need anything? Have they looked at this library? Could gaps in their research benefit from our collection?'." The team's current collaborations includes creating a molecular glue library, both via vendors and in-house synthesis, with multiple faculty across St. Jude and CBT. Recently, the the team made available a Mechanism of Action Library (MOA), which consists of 2050 small molecules, covering over 1,000 primary gene targets.



Lastly, Gisele mentions feedback as the number one desire of her team. Understanding what others need will help the compound collection meet the challenges and demands in the ever-evolving world of screening in academia.

Lead Discovery Informatics

Chemo-centric informatics infrastructure for St. Jude, enabling a deeper interrogation of biology through the integration of chemistry, computation, and data science

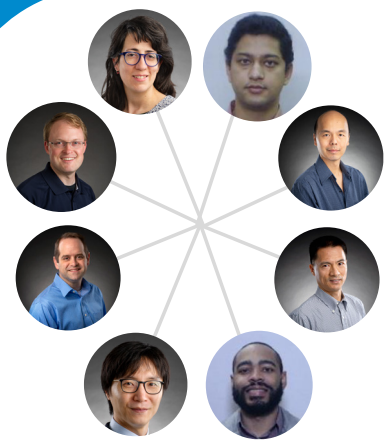
Lead Discovery Informatics (LDI) is composed of a team of scientists with expertise in computational chemistry, chemical informatics, bioinformatics, applied mathematics, and computer science. LDI performs molecular modeling and simulation, builds databases that integrate chemical and biological data, supports Compound Management with tools for chemical registration and searching, creates software for processing and visualizing complex data, and helps maintain and enhance the institution's world class compound library. LDI strives to enable a deeper interrogation of biology through the integration of chemistry, computation, and data science. LDI works closely within CBT, and with diverse groups at St. Jude and beyond, using our knowledge of chemically aware computation to help design, execute, and analyze experiments. LDI is led by faculty member ***Anang Shelat.***

"We are pioneering new solutions to tackle novel and difficult targets for small molecule drug discovery. We are developing and applying our expertise in the areas of machine learning, ultra large scale docking, and the design of next generation small molecule-DNA modulators. These efforts push current boundaries and speed projects to successful outcomes."

- Jason Ochoada, Cheminformatics Scientist

"CBT has shown me that there is a huge opportunity for growth in the way scientific data is analyzed and shared. Many scientific departments don't have a dedicated team of informatics scientists working hand in hand with researchers on the tools used to analyze their data, and so most researchers necessarily rely on simple or out-of-the-box tools. In CBT, however, we have the opportunity to customize the tools we use to analyze experimental data, and fully realize the potential of those experiments. It's really exciting."

- Nathaniel Twarog, Cheminformatics Analyst



High-Throughput Biosciences

Target identification and validation, assay development, high- throughput and high-content screening, 3D cell culture, experimental automation, and management of scientific collaborations

HTB

For the past 15 years, **High-Throughput Biosciences** (HTB) has been making St. Jude researchers' scientific projects come to life by aiding in assay development, assay validation, miniaturization, and automation. HTB is run by a team of scientists with advanced biological, chemical, and engineering expertise who bring their talents together to produce great results through numerous assays and projects. HTB takes those assays and scales them to a high-throughput capacity using the robotic systems within the lab which can obtain greater amounts of data in shorter time frames with no additional manpower. HTB is well known for housing four large robots used for screening and automation: Max, Saver, Billy, and Widget. They also previously managed Clifford, a compound storage and automation robot. HTB is constantly working on collaborations with St. Jude investigators. Over the past 10 years HTB collaborated with an average of 31 laboratories each year, generating over 28 million high-quality data points across 150,000 assay plates. The High-Throughput Biosciences Center is led by faculty member ***Taosheng Chen.***

"There are eight of us, so we can cover projects from multiple directions. The brainstorming sessions we have are fantastic. We can take someone's idea and turn it into something reproducible and screenable. We have all the tools of a well-funded biotech which makes us incredibly flexible. If you can imagine it, we can probably find a way to make it happen."

- Jonathan Low, Senior Scientist

"These systems are made up of various pieces of equipment that work together using integration software to fully automate assays/ workflows that were previously 100% manual or semi-automated. Before coming to St. Jude, I had worked with platforms that were considered semi-automated, but nothing as robust as what I have worked with in HTB. Being able to see the impact of my work on the lives of many is one of the things that makes my job so fulfilling."

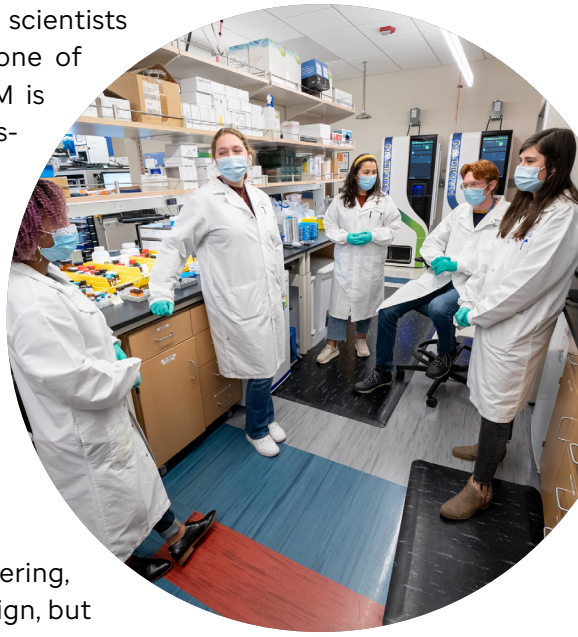
- Marlon Trotter, HTS Automation Technologist

Compound Management

Curates the St. Jude small molecule library using state-of-the-art automation and electronic data management systems

CM

One of the most unique collaborative resources at St. Jude is a group of scientists and engineers, the **Compound Management** team (CM) who curate one of the largest small molecule libraries in academia (> 600K compounds). CM is one of the few centers that brings in local students and gives them hands-on experience doing what they do best which is acquisition, registration, quality control, storage, retrieval, formatting, and delivery of compounds to St. Jude researchers for biological screening and pre-clinical research. CM is a part of numerous projects happening at the hospital – providing chemical samples in several formats. Delivery of the compounds at the correct concentration and format in an efficient manner is vital to the accuracy of researchers' experiments and a project's success. Compound Management is led by Research Operations Director ***Julianne Bryan.***



"I came into my degree, biomedical engineering, thinking I was going to go into product design, but CM has provided me the opportunity to try out new things. It has reframed my perspective on what a biomedical engineer can be, and I think it's impacted how I perceived myself and my career trajectory."

- Andrew Williams, Compound Management Student

"We create an environment for acquiring molecules easier, so investigators can focus on the research. We know where to look and who provides the best samples. We also collaborate with other CBT centers to ensure their quality and integrity."

- Shalandus Garrett, Senior Researcher

"We are able to be a part of that driving force that can provide resources for different collaborators and help get their research started. So, that's really cool that we can kind of dip our toes in a lot of different areas."

- Mariana Santana Ponce, CM Automation Technologist

Medicinal Chemistry

Identification and development of potent and selective small molecules to investigate disease-related biological targets in cells and in vivo preclinical models

MCC

The **Medicinal Chemistry Center** (MCC) is known for designing, synthesizing, or identifying small molecules for researchers at St. Jude. MCC synthesizes molecules of interest that are not available for purchase and provides an internal source of chemical matter and evidence to support ways to build molecules. Typically, MCC helps researchers find relevant literature-disclosed probes from (conferences, scientific journals, or patents) and arrange for their purchase or synthesis if commercially unavailable. They also engage in a hypothesis-driven research effort to provide novel chemical probes for targets where such molecules do not exist. MCC makes an effort to examine and utilize the most novel, cutting-edge steps to make things as efficient as possible in the compound creation process. The Chemistry Centers are led by ***Zoran Rankovic*** and the Medicinal Chemistry Center is led by ***Brandon Young.***

"There are so many bright people around here that you can just pick someone else's brain. He or she's more than willing to kind of support you and help you out, give you an alternative perspective of things. It's a cycle of chemistry, biochemistry, biology, and back to chemistry – really a Disneyland for scientists."

- Jake Slavish, Senior Scientist

"Getting a hit is just the beginning of the process. Most compounds have to be optimized further to show any sort of activity, so you really have to commit yourself to the long game if you're going to look for new chemical matter. We constantly ask ourselves, 'Is this the best molecule we can make, or is there something we can do to improve it?"

- Brandon Young, MCC Lead Scientist

The CBT Chemistry Centers consist of three highly integrated teams that collectively provide state-of-the-art small molecule chemical probe design, synthesis, and analysis capabilities: Analytical Technology Center (ATC), Chemical Biology Center (CBC) and Medicinal Chemistry Center (MCC).

CBC

Chemical Biology

Develop sophisticated chemical tools to map and interrogate biological and pathological pathways

The **Chemical Biology Center** (CBC) focuses on developing chemical tools to map disease pathways. The CBC toolbox includes PROTACs, molecular glues, pull-down, photoaffinity, and imaging probes. They also have experience developing and utilizing biochemical assays, including fluorescence polarization (FP), time-resolved fluorescence energy transfer (TR-FRET), AlphaScreen, and cell-based assays. The Chemical Biology Center supports and collaborates with investigators who need expertise in chemistry or chemical probe discovery who may have more biological backgrounds. They develop and define strategies to investigate novel targets from different types of approaches. CBC is taking on cancer research through a small molecule lens. The Chemistry Centers are led by ***Zoran Rankovic*** and the Chemical Biology Center is led by ***Gisele Nishiguchi.***

"We reach out to researchers and ask, 'What do you think of this target? Do you think it is druggable? Can we find a small molecule? Can we find a chemical probe?' We're here to support and collaborate with the researchers within St. Jude and other PIs that have expertise in biology or pharmacology that don't have the expertise in chemistry or chemical probe discovery."

- Gisele Nishiguchi, CBC Lead Scientist

"The people that make up our CBC group are very supportive. I was originally trained as a chemist, but I get to learn various biochemical techniques and am always encouraged to keep learning. That's a cool environment to experience. We move compounds from initial discovery to optimization. It's a lead kind of process to improve compound properties. And beyond that, we're able to contribute with biochemical screens to understand better how compounds work."

- Marisa Actis, Senior Researcher

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Analytical Technologies

Provide an extensive battery of assays designed to evaluate compound, chemical, biochemical, biophysical and ADME properties

ATC

The **Analytical Technolgies Center** (ATC) develops highly customized bioanalytical methods, formulations for in vivo studies, mass spectrometry-based biochemical assays and tissue imaging, with experience in natural product extract fractionation, high-throughput library purification, and structure determination. ATC helps researchers understand the intensity, purity, and chemical properties of compounds based on their data. ATC generally provides high-throughput analytical support and even develops customized assays depending on a researcher's requirement or special needs. ATC routinely assists collaborators through coordinating work with other CBT centers by providing consultations and defining project strategies. The Chemistry Centers are led by ***Zoran Rankovic*** and the Chemical Biology Center is led by ***Lei Yang.***

"My favorite aspect about working in ATC is that I can provide precise and accurate data for my colleagues that will help them to understand their compounds and optimize leads. It's always a challenge – using all your knowledge and skills to make particular assays work for a difficult target compound."

- Lei Yang, ATC Lead Scientist

"ATC generally provides high throughput analytical support to researchers and investigators in CBT and across the campus, depending on the lab's requirement. Working in ATC has indulged me with a broad experience in translational research. I became familiar with the entire drug discovery process from synthesis to screening, to preclinical studies."

- Divyabharathi Chepyala, Senior Researcher

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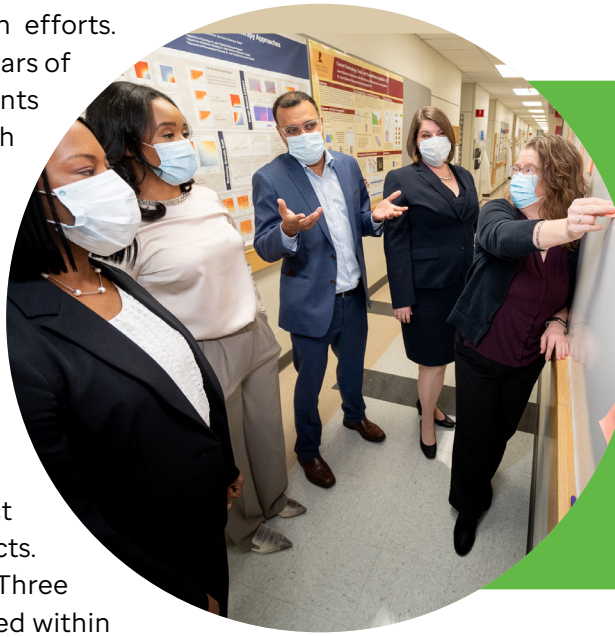
Project Management Office

PMO

Implement project management practices and methodologies in the drug discovery process from bench to bedside and provide project management to support St. Jude investigators.



At the center of the CBT machine, there's an interdisciplinary team of scientists who work as project managers (PMs) to support the department's collaboration efforts. Every member of the **Project Management Office** (PMO) has over 9 years of experience at the bench; designing, conducting, and analyzing experiments resulting in publications in top-tier journals. This experience together with Project Management Professional (PMP) certification is part of the unique environment at CBT and St. Jude. The PMO team implements project management practices and methodologies into the translational drug (lead/tool/pre-clinical) discovery process from bench to bedside. They have designed and built systems that are utilized by researchers across campus to accelerate bench discoveries for use in the clinic. The PMO-created system is designed to produce an environment that generates knowledge, allows information capture, enhances communication, and provides faster process turnarounds to reduce project timelines. The Project Managers also facilitate the establishment and tracking of project objectives, milestones, and budgets across multiple concurrent projects. Collaboration is a huge cornerstone of the Project Management Office. Three of the programs in the Comprehensive Cancer Center are also represented within the PMO by three of the PMs who work closely with preclinical trials to accelerate discoveries to the clinic. The PMO implements project management practices as defined in the Project Management Body of Knowledge® into the drug discovery process. Using the Project Management Institute's standards and practices as a basis, the PMO has created a system, unique to CBT and St. Jude, that performs well in an academic research environment. The PMO is led by Research Operations Director, ***Julianne Bryan.***

"PMO specializes in informed decision making and supporting efficient project completion while avoiding scope creep (staying on track). I like to think that we provide priorities, structure meetings, and help remind everyone what needs to be done in a timely fashion to complete a successful project. I think the best aspect of my job is that I get to be a part of doing something good for other people. And a lot of my job is to share what we know for free and that's an amazing opportunity."

- Asa Karlstrom, Program Manager

"We are primarily responsible for the coordination and monitoring of the progress of CBT collaborative research projects. We often function as the liaison between all the centers and others. We are always available for collaboration. The best method we use is to identify your CBT collaborative project, then your project management need. We are happy to offer project management support."

- Sharnise Mitchell, Program Manager

Beyond CBT Borders

Across St. Jude & the Globe

CyberTea

CBT CyberTea has evolved from a casual place to build relationships among department members to an outlet for CBT to learn about professional development opportunities and engage in thought provoking scientific discussions with potential collaborators.

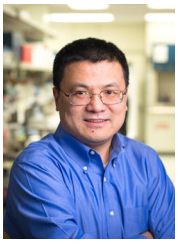
Over the past few months, priorities within the department have shifted and CyberTea now focuses solely on sharing provocative scientific ideas. Each month CyberTea features a potential collaborator within St. Jude and after the session, CBT's Research Operations Manager, Carolina Adura, will connect the individual with CBT leadership to formulate a plan for engagement. Overall, we hope that these CyberTea sessions will foster collaborations and lead to scientific breakthroughs. Read more about how you can collaborate with us on page 5.

Outside-the-Box Sessions

Brainstorming sessions between CBT and researchers at St. Jude happen every month. At these sessions our department engages colleagues across St. Jude to work together to delineate clear chemical biology strategies to further our understanding of the biological mechanisms in childhood diseases. The larger goal is to translate this knowledge into new therapeutic opportunities. The collaborative centers at CBT play a crucial role in this endeavor by using cutting-edge technologies in highthroughput screening, bioinformatics, compound and liquid handling, project management, and medicinal chemistry among others.

"The resources and knowledge contained within CBT are invaluable to researchers at St. Jude looking to advance their science towards clinical application. When we reached out to CBT regarding potential collaborations, we were thrilled to find a clear pipeline in place to facilitate the process. Faculty and staff from CBT engaged thoughtfully with our science during a pre-consultation meeting, allowing us to identify crucial next steps and points for collaboration. The collaboration pipeline at CBT has certainly smoothed the path forward for us to test the therapeutic potential of our discoveries and we are grateful for it."

Shannon McKinney-Freeman, PhD - Associate Member
& Chris Nevitt, PhD - Postdoctoral Research Associate
Department of Hematology



"It was really wonderful and productive to engage with CBT and participate in the CyberTea and pre-consultation brainstorming sessions. Moreover, from these processes, we have learned many powerful, cutting-edge technologies and resources at CBT, and received valuable suggestions from faculty on various other projects in the lab. Overall, we have had incredible experiences collaborating with CBT!"

Hongbo Chi, PhD - Member
Department of Immunology

Grants

Over the span of two months last fall, CBT displayed incredible teamwork by successfully assembling and submitting a 883-page international D43 training grant led by the CBT Chair, Aseem Ansari. CBT collaborated with internal partners, as well as partners from all corners of the U.S. and India. The proposal consisted of 12 institutions and 93 investigators. The consortium that was formed led to the signing of memorandum of understanding between St. Jude and CSIR, the largest scientific agency of the Government of India. The partnership will facilitate collaborative projects on sickle cell diseases, cancers, and leveraging artificial intelligence and data sciences for healthcare.

On a different note, pre- and post-doctoral Fellows are encouraged to apply for funding opportunities! Prospective applicants should consult with their mentor and meet with Roxy Chirlow, CBT's grants coordinator for one-on-one training on internal processes. Prospective applicants are also advised to contact the Program Officer identified on the funding announcement to discuss the relevance of proposed research to the institute's research priorities. The Program Officer will provide guidance on the proposed research and training plans and help identify the most appropriate funding opportunity for research and training. CBT has recently submitted an F31, F32, Damon Runyon Fellowship, and K99/R00. There are many opportunities available. A special congratulations to Marcus Fischer who recently received the R35 Maximizing Investigators' Research Award and Tommaso who was nominated for the Searle Scholars Program and Rita Allen Foundation Scholars Program!

2021 Speakers

Aled Edwards - Structural Genomics Consortium
Eranthie Weerapana - Boston College
Behnam Nabet - Dana-Farber Cancer Institute
Paul Thompson - University of Massachusetts
M. Madan Babu - St. Jude Children's Research Hospital
Jiyang Yu - St. Jude Children's Research Hospital
Jun J Yang - St. Jude Children's Research Hospital
Jen Heemstra - Emory University
Rivka Dikstein - Weizmann Institute of Science
Danette Daniels - Promega
Jun Qi - Dana-Farber Cancer Institute
Sara Buhrlage - Dana-Farber Cancer Institute
Paul Geeleher - St. Jude Children's Research Hospital
Luiz Pedro Carvalho - Crick Institute
Geeta Narlikar - University of California, San Francisco
Stacey Finley - University of Southern California
Carme Rovira - University of Barcelona
Kathrin Lang - ETH Zurich
Mia Huang - Scripps Research
Rebecca Wade - Heidelberg Institute for Theoretical Studies
Mustafa Guzel - Istanbul Medipol University
Jie Zhou - University of California, San Francisco
Jiankun Lyu - University of California, San Francisco
Martin Burke - University of Illinois at Urbana-Champaign
Amy Barrios - University of Utah
Caitlin Davis - Yale School of Medicine
Brittany Morgan - University of Michigan
Christopher Parker - Scripps Research

2022 Speakers

Keriann M. Backus - University of California, Los Angeles
Alice Y. Ting - Stanford University
Dustin J. Maly - University of Washington
Jennifer Brodbelt - University of Texas at Austin
Alison Axtman - University of North Carolina at Chapel Hill
Sheila S. David - University of California, Davis
Yan Jessie Zhang - University of Texas at Austin
Lindsey I. James - University of North Carolina at Chapel Hill
Fred Guengerich - Vanderbilt University
Dylan Taatjes - University of Colorado Boulder

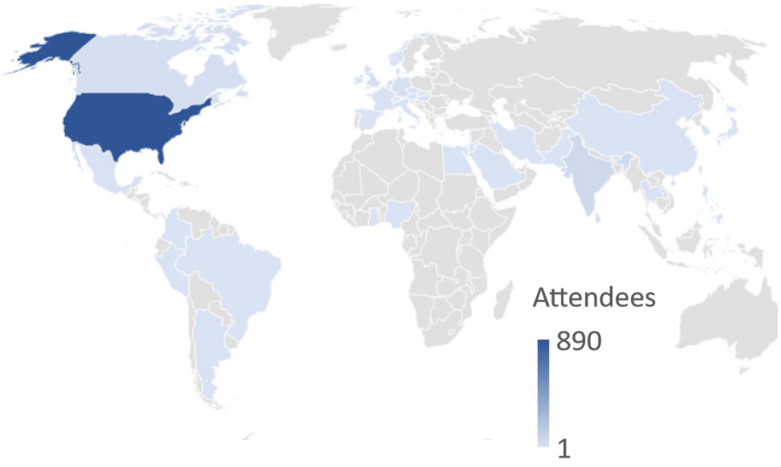
BRINGING CHEMISTRY TO MEDICINE

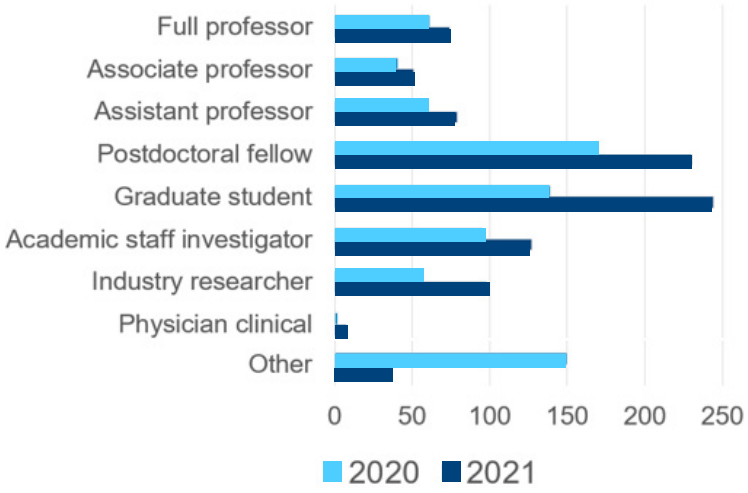
Across The Globe

In July 2021, Chemical Biology and Therapeutics joined forces with the Comprehensive Cancer Center to host the second annual **Bringing Chemistry to Medicine Symposium**, delivered on an entirely virtual platform. The event featured high-profile experts in the fields of transcription therapy and chemical biology. Following the success of the 2020 virtual symposium, the event was hosted and moderated by Aseem Ansari, Chair of CBT, and **Charles Roberts**, Director of the Comprehensive Cancer Center. The Transcription Therapy talks on day one were grouped into two sessions: Chromatin and Epigenetics and Transcriptional Machinery. The Chemical Biology talks on day two featured topics in Computational Biology and Frontiers in Chemical Biology. Panel discussions provided invigorating discourse on the topics and allowed attendees to interact with highly regarded researchers.

Both events had the benefit of planners Carole Weaver, Cancer Center Program Director; Ellie Durbin, CBT Administrative Assistant II; and Natalie Racine, CBT Administrative Director and major support from Anna Acerra, Director of Digital Integration; Lauren Sides, Administrative Specialist; Carrie Strehlau, Senior Social Media Specialist; and Erin Seidler, Senior Director of Public Relations. Madison Rice, CBT's Scientific Visualization Engineer, provided graphics for the website, abstract book, and attendee communications. Notable attendees joined from journals including JACS and Nature Genetics and pharmaceutical companies such as Lilly, Bristol Meyers Squibb, Merck, Novartis, Pfizer, and Sanofi. Past speakers for the 2020 conference also joined the 2021 symposium.

2021





Registrants	**1,600**
Attendees	**1,100** Unique **1,200** Transcription Therapy, 800 CBT
Institutions	**>250**
Countries	**41**

Join Us:

Bringing Chemistry to Medicine 2022

July 21st & July 22nd

TRANSCRIPTION THERAPY

DAY 1

Suzanne J. Baker
St. Jude Children's Research Hospital
Histone Mutations and Disrupted Development in Pediatric High-Grade Glioma

Patrick Cramer
Max Planck Institute for Biophysical Chemistry
Recent Insights into Chromatin Transcription

Jonathan D. Licht
University of Florida Health Cancer Center
NSD2 in Lymphoid Malignancy

Cigall Kadoch
Dana-Farber Cancer Institute
Structure and Function of Mammalian SWI/SNF Chromatin Remodeling Complexes in Human Cancer

James E. Bradner
Novartis Institutes for Biomedical Research
Chemical Control of Gene Expression

William G. Kaelin Jr.
Dana-Farber Cancer Institute Three
Possible Paths to Targeting Undruggable Transcription Factors

Andrea Califano
Columbia University
Elucidation and Pharmacologic Targeting of Single Cell State Maintenance Mechanisms

Anjana Rao
La Jolla Institute for Immunology
Transcriptional Networks in Tumour-Infiltrating T Cells

Mitch A. Lazar
University of Pennsylvania
Personalization of Transcriptional Therapy With Drugs Targeting Nuclear Receptors

FRONTIERS IN CHEMICAL BIOLOGY

DAY 2

Pedro R. Cutillas
Barts Cancer Institute
Rationalising Anti-Cancer Drug Responses Using Proteomics and Machine Learning: Towards Next Generation Precision Medicine

Francesca Ciccarelli
King's College London
Predictors of response to cancer immunotherapy: beyond Tumour Mutational Burden

Anang A. Shelat
St. Jude Children's Researh Hospital
Using Response Surface Models to Analyze Drug Combinations

Tobin R. Sosnick
University of Chicago
Prediction of a Protein's Free Energy Surface with Validation Using Hydrogen/Deuterium Exchange

Janet Thornton
European Molecular Biology Laboratory
Computational Enzymology: The Structure, Function and Evolution of Enzymes

M. Madan Babu
St. Jude Children's Research Hospital
Variation in GPCR Signalling: Implications for Drug Discovery

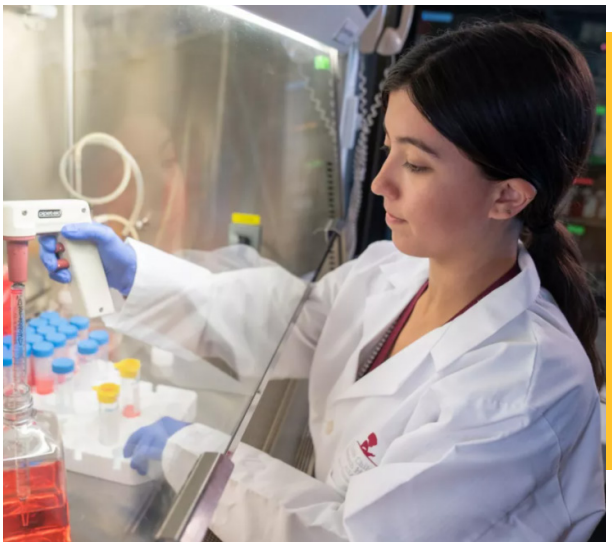
Craig W. Lindsley
Vanderbilt University
Discovery and Development of GPCR Allosteric Ligands: From Concept to Clinic

Marvin J. Miller
University of Notre Dame
Design, Syntheses and Studies of New Antibiotics

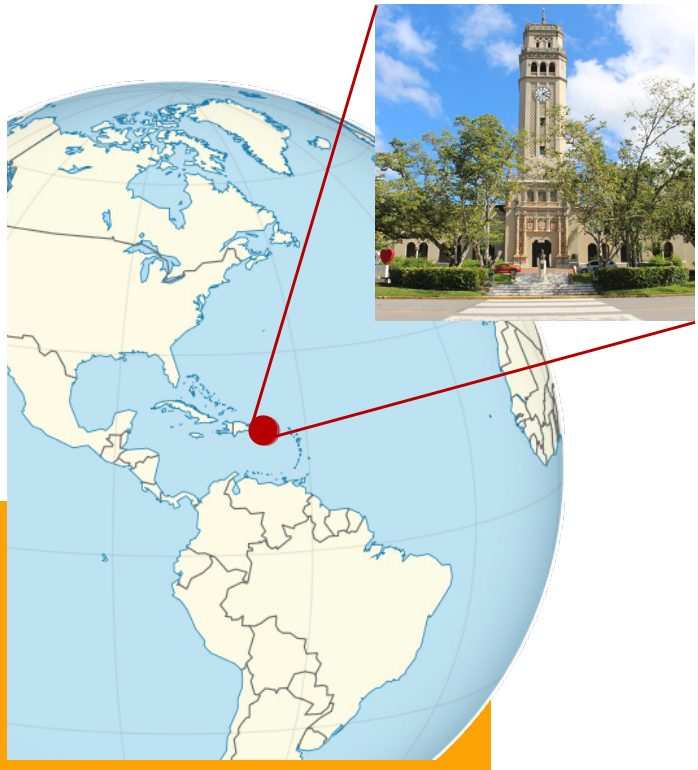
Craig M. Crews
Yale University
PROTAC-mediated Protein Degradation: A New Therapeutic Modality

Nurturing Talent

In June of 2020, CBT lost a beloved member, Dr. **Nancy Martinez**, unexpectedly in an accident. Nancy was incredibly fun and boisterous, often filling the halls with her laughter. While remembered her for her bubbly personality, we later learned from her former colleagues about her struggles during her education, typical of a first-generation American student. To be close to home, she went to a very small school to earn her bachelor's degree. While this was ideal for her family, she missed opportunities offered at larger schools like working in a lab or participating in research. Despite this disadvantage, her aptitude for science allowed her to continue to graduate school and eventually join St. Jude as a postdoc. In her honor, we developed a program to provide support and opportunity to students like Nancy who have great potential but could use additional resources to succeed.



The spring semester of 2021 launched the virtual pilot course ***Principles in Biomedical Research***. This course was held at the University of Puerto Rico in Rio Piedras by former Ansari Lab post doc, Dr. José Arcadio Rodríguez-Martínez, currently an Assistant Professor of Functional Genomics at UPR-RP. Developed by **Natalie Racine** (Administrative Director, CBT) with the help of **Fatima Rivas** (former Assistant Member, CBT), **Sally MacIver** (Director of Academic Programs), and **Kate Ayers** (Manager of the Cancer Education Program), the syllabus was an introduction to modern biomedical research with a focus on targeting cancer in the context of complex biochemical environments and aberrant overexpression of oncogenes. Under this overarching topic, Teaching Assistant **Ana Vazquez-Pagan** (St. Jude Graduate School student) led thirty students through concepts such as the scientific method, reading and interpreting scientific literature, basic laboratory practices, writing a research proposal, and developing a CV, all while hosting lectures by St. Jude Faculty Members. The course ended with a panel of Latinx scientists in various professions to provide ideas on research career options.



At the end of the semester, students were invited to submit a research proposal and personal statement to compete for two internship opportunities. The two students who were selected spent ten weeks virtually with the Ansari Lab working on a computational-based research project. The students received a stipend sufficient to support themselves during this period, a crucial component to providing educational opportunities in this community.

The course was well-received by students who took it at UPR-RP with a waitlist already established for the upcoming semester. We plan to partner with additional institutions in the coming years and hopefully obtain enough funding to host more in-person summer interns. In providing this type of opportunity in Nancy's honor, we aim to encourage the curious young minds of underrepresented minorities to pursue careers in research—maybe even at St. Jude someday, just like Nancy.

Scientist Highlight: Shanshan

When asked why she became a scientist, Shanshan Bradford, Lead Researcher in the Fischer Lab, puts it best. “I want a challenge. I’m just crazy about biology. Watching cells, their cycles, chromosomes all working together you think - ‘that’s amazing! Why is this happening? What are the mechanics behind it?’ - that kind of discovery pushes me to keep thinking.”

Shanshan has been at St. Jude since 2009, where she first worked in the Schulman Lab studying the enzymatic mechanism of a large E3 ubiquitin ligase complex, while pursuing her PhD as a UT graduate student. From 2016 to 2017 she worked in the Enemark Lab, helping to solve the structure for DDX3x-RNA complex, a DEAD-box RNA helicase. She then joined CBT. In the Fischer Lab, she has been involved in projects studying HSP90 inhibitors and the Jak2 kinase, guiding novel inhibitor search and design. Now, she drives research projects and maintains lab operations. Her colleagues at CBT describe her as a bubbly, hard-working straight shooter. “One of my best memories working with Shanshan was collecting hundreds of room-temperature datasets in the graveyard shift at the synchotron,” says Marcus Fischer, “she’s a tenacious and determined person to work with.”

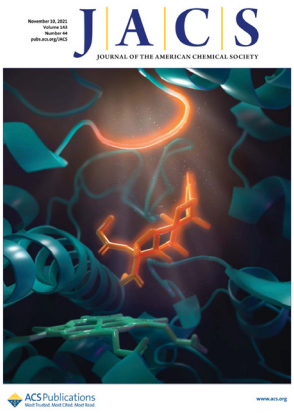
Shanshan grew up in Wuhan, China and went to college in the Capital of Beijing. “My hometown is located where two rivers meet and has very similar summer weather to Memphis, humid and hot,” she explains. In their free time, Shanshan and her husband enjoy brewing beer together, and are passionate about the process. “I studied fermentation bioengineering in college, so I understood many food fermentation processes like brewing beer, wine, and making yogurt. It’s similar to what I do in a lab – finding optimal conditions to grow, finding the right nutrients to produce a flavor, etc. You cook stuff, you sanitize stuff, and then you transfer one container to another,” she says. Shanshan also enjoys movies, running, playing with her dogs, and camping. Recently, she’s also taken up coding in Python.

“It’s kind of interesting we can communicate with the machine and let the machine do the work for you. That’s really powerful.” Shanshan has recently finished a master’s degree in Information Systems. Over time she grew more interested in data analysis and management and the opportunities to apply them to her research. “I started thinking, ‘why can’t I automate these programs myself?’ The research community has so much data piled up. We can use machine learning to dig up patterns to tackle it all, and save us time.”

In addition to brewing her own beer with her husband, exploring data science, and working in the lab, Shanshan is a bright, inspiring part of the CBT family.

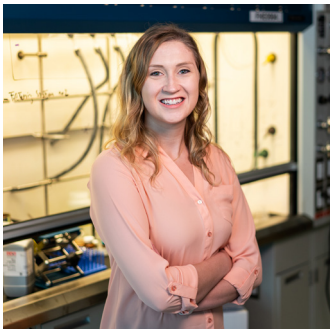
CBT Research

The **Ansari Lab** is collaborating with multiple colleagues at St. Jude to target a wide range of genomic loci with synthetic DNA binding molecules. To meet the highly diverse and still growing portfolio of exciting projects, the group welcomed Suresh Kandikonda and Nilanjana Chowdhury, two synthetic organic chemists. The synthetic team further benefitted from the active engagement by a visiting Fulbright Scientist, Prof. Jaisankar Parasuraman, who brought a lifetime of experience as a chief scientist and chair of medicinal chemistry at the Indian Institute of Chemical Biology. Together the team has rationally designed and synthesized an array of promising synthetic genome readers and regulators (SynGRs) that are already providing unprecedented chemical control over target gene regulation. In parallel, the prototype SynGR, named SynTEF1, is maturing as a potential therapy for Friedreich's ataxia.

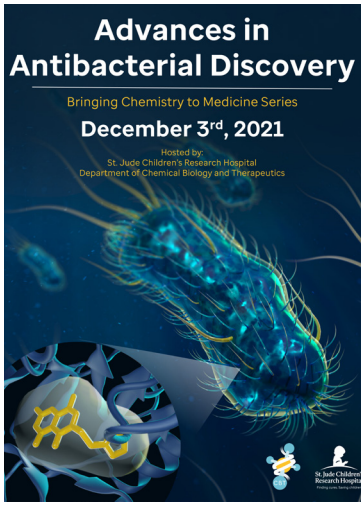


The **Chen Lab** used the most important human drug-metabolizing enzymes, cytochrome P450 (CYP) 3A5 and 3A4 which metabolize more than half of marketed drugs, as models to tackle a challenging task. Because CYP3A4 plays predominant role in hepatic drug metabolism and its inhibition may cause adverse drug-drug interaction, the mechanism for selective inhibition of CYP3A5 is needed to distinguish its role from that of CYP3A4 and guide the development of potential therapeutics. The lab discovered clobetasol propionate as the first selective CYP3A5 inhibitor and used it as a tool compound to discover a unique conformation of a surface loop of CYP3A5 that enables the selective binding of the inhibitor. These efforts support the feasibility of selectively inhibiting the highly homologous CYP3A family enzymes to control therapeutic responses. The findings were published in November 2021 in the *Journal of the American Chemical Society* and featured a supplementary journal

The newly formed **Cupido Lab** welcomes Katelyn Baumer (PhD from Baylor University), who is the first post-doc to join the lab. The lab has focused on developing robust biochemistry-based assays to identify a new class of bio-active compounds that can be used as probes for molecular mechanisms of chromatin organization. The Cupido Lab is set to discover inhibitors and allosteric modulators of RNA/DNA-dependent ATPases. These ATPases compose a class of biochemically diverse and structurally related enzymes that have recently emerged as crucial regulators of genome structure and function, but their precise roles and regulation are still poorly understood. With help from the Structural Biology Department at St. Jude, the lab is now working at the interface between synthetic chemistry, biochemistry and cell biology to understand how these important molecular motors can be targeted with small molecules, and the rules of engagement that will allow the generation a new class of selective chemical probes to study genome function.

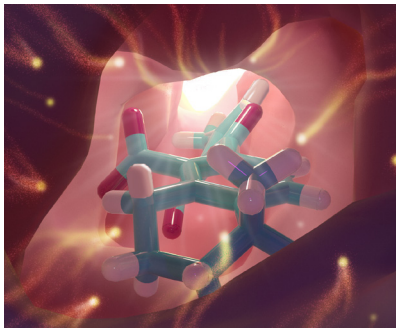


The **Fischer Lab** has published eight papers in 2021. Shanshan Bradford's article "Temperature Artifacts in Protein Structures Bias Ligand-Binding Predictions" has been picked up by several news outlets and landed on the cover of Chemical Science. Fatemeh Keramatnia, PharmD, PhD, our joint student with the Chemistry Centers, has received an Alma and Hal Reagan Fellowship for her graduate work on Targeted Protein Degradation. In August, we welcomed our new postdoc Sarah Young to the lab. Sarah will drive the structural biology of the Crazy8 initiative that explores small molecule degraders for targeting transcription factor drivers of childhood cancers. Finally, we were thrilled to receive major NIH funding for our R35 MIRA grant on "Exploiting Water Network Perturbations in Protein Binding Sites" that Tim Stachowski is working on.

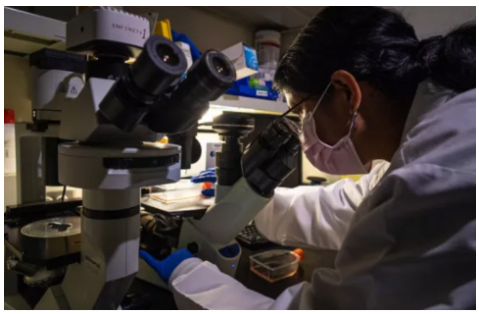


The **Lee Lab** has made significant accomplishments since the last newsletter. The lab generated their 5,000th molecule to advance into biological testing. Compound BBP-671, first synthesized in the lab, entered clinical trials as a first-in-class PanK modulator. The lab also hosted the Advances in Antibacterial Discovery Conference on December 3rd, an event within the Bringing Chemistry to Medicine Series, highlighting our interest in tackling the growing problem of antimicrobial resistance using advanced chemistry. This symposium attracted 540 attendees from 34 countries.

The **Potter Lab** developed a series of tetrahydroquinoline analogs that are potent and selective bromodomain inhibitors, targeting the BD2 domain in the BET family of proteins. Following extensive chemical, biochemical biophysical and molecular analyses, a candidate, SJ432, has been developed that demonstrates excellent antitumor activity both in vitro and in vivo, but demonstrates much reduced toxicity towards normal cells. Very recent studies have confirmed the efficacy of SJ432 towards pediatric xenografts and this compound appears more potent than comparable molecules designed by pharmaceutical companies that are currently in clinical trials. We anticipate that SJ432 will be an effective lead for the treatment of pediatric tumors.



The **Shelat Lab** is involved in several translational research projects in pediatric cancer. Jia Xie and Teneema Kuriakose confirmed the therapeutic potential of ATM inhibition to improve the efficacy of radiation therapy in pediatric high grade glioma. In the process, the team also discovered a novel mechanism of resistance to this combination therapy, which involves bypass of the ATM pathway and concomitant synthetic lethality with ATR inhibition. Debolina Ganguly identified XBP1 as a potential driver of resistance to replicative stress in pediatric sarcoma cells. Anasuya Pal, who joined the lab in January as a post-doctoral fellow, is exploring the therapeutic potential of bromodomain-selective BET inhibition in treating pediatric cancer. In previous work, the Shelat and Potter Labs worked with the CBT Centers to develop a bromodomain-selective BET inhibitor, SJ432, which shuts down MYC expression in neuroblastoma cells and delays neuroblastoma tumor growth in mice with minimal toxicity. Evan Savage joined the lab as a bioinformatics research scientist in April. Evan is using machine learning applied to genomic scars to detect defective DNA repair processes in cancer cells.



Remembering Michele

Friends and colleagues remember **Michele Connelly** as a dedicated scientist, a thoughtful coworker and a kind-hearted individual. Connelly, an Associate Scientist in Chemical Biology and Therapeutics passed away on April 10, 2021 after a long battle with cancer. She worked at St. Jude for more than 40 years. Martina Sigal, a close friend of Michele's, remembers her here:

"I still remember the day that I met Michele. It was early 2006 and CBT was in its infancy. Chair Kip Guy introduced Michele to his two senior lab members and told us that she was a long-time St. Jude employee with exceptional knowledge of tissue culture and biological assays. He asked us to chat with her, and though it was nothing like the thoroughly organized job interviews of later years, it led to one of CBT's best and most fruitful hiring successes. Michele and her two brothers grew up in Illinois. Early on, she loved biology and had a particular interest in botany. When it came to plants of the Midsouth, Michele was my Google. She taught me when to prune azaleas and why Lenten roses are called Lenten roses. In her own words, it was her love of biology that brought her to Memphis, where she enrolled at University of Memphis for a master's degree in biology. After graduation, she tried out for a job at St. Jude – and the rest is history, as they say. Michele started as a Research Technologist in the Department of Pharmacological Sciences in December 1979. Forty years later, the CEO of the hospital called the now Associate Scientist to the stage of the Peabody Hotel's Grand Ballroom to acknowledge her exceptional

anniversary. What lay in-between were many work hours spent in the departments of Infectious Diseases, Developmental Neurobiology and finally CBT, all to the benefit of the children of St. Jude and beyond.

Michele was always thinking about work, sometimes to the detriment of thinking about vacations. Her favorite pastime was spending time with her relatives, particularly the five nieces and nephews. There was not a milestone in their lives that she missed. And she was beloved in return. Visits to or by Aunt Michele were always favorites.

She spoiled them with exciting activities, like visits to the Zoo, the Children's Museum, or the ice cream parlor. Later, she secured summer jobs at St. Jude or ALSAC for the young adults. Michele was a unique and highly motivated individual. She cared for her coworkers and provided outstanding service to her labs and departments. Michele truly embodied the mission of St. Jude."

Cations and Anions

HAI DAO

CBT introduced a new faculty member to the department this year, **Hai Dao**. Dao's expertise in synthetic organic chemistry and his training in chromatin biology enable him to explore the role of chromatin dysfunction in catastrophic pediatric diseases. The confluence and complementarity of skills uniquely position him to thrive and contribute to the scientific efforts across St. Jude as well as enrich the synthetic depth of CBT. Dao received his undergraduate degree in chemistry from the University of Tokyo. He conducted predoctoral research with Professor Shū Kobayashi on cooperative catalysis exploiting the dual properties of Indium(I) catalysts. Dao's talent and academic accomplishments were rewarded with the prestigious Fulbright S&T fellowship that enabled him to pursue his doctoral studies with Professor Phil Baran at The Scripps Research Institute (TSRI). There, Dao applied rhodium and iron based catalysts for steroid synthesis and selective olefin functionalization. A 2016 Jane Coffin Childs fellow, Dao joined Professor Tom Muir's group at Princeton University. There, he transitioned from organic chemistry to chromatin biology, investigating molecular interplay between chromatin and ATP-dependent remodeling complexes in collaboration with Professor Cigall Kadoch at the Harvard Medical School/ Dana Farber Cancer Institute. Dao's expertise in organic synthesis when combined with mass spectrometry resulted in a "photoscanning" approach that enabled the capture of the regions of the ATPase domains that interact with the nucleosome.

PHIL POTTER

After 31 years of distinguished service to St. Jude, Phil Potter has announced his retirement this summer. Phil obtained his Ph.D. from the Patterson Institute for Cancer Research at the Christie Hospital in Manchester, UK. He joined St Jude as a postdoctoral fellow in the Department of Molecular Pharmacology in 1991. His expertise in molecular biology led to rapid promotion to the faculty in 1993 and subsequent rise to associate member in 1999. In 2010, Phil joined the new Chemical Biology and Therapeutics Department as the eighth faculty member. Highlights of his career include over 240+ published articles and patents and over 25 years of continuous NIH grant support. His research has focused on the role of carboxylesterases, which are critical drug metabolizing enzymes vital to the efficacy and safe use of many medicines. Phil has been a great team player and mentor to his research team and junior faculty members. Phil is leaving with the great respect of his peers, feeling this is the right time to step down; "Recognize when the young scientists are smarter than you and let them lead! That's why I am gracefully retiring!" – Phil. He is looking forward to traveling, spending time in France and the UK with family and friends, and pursuing his interests in woodworking, good food, and good wine.

DR. JAI

Last September, Professor **Parasuraman Jaisankar** (Jai), viewed the inaugural St. Jude Transcription Therapy Symposium from his office at the Indian Institute of Chemical Biology (IICB) in Kolkata. The 2020 symposium left an indelible impression upon Jai. The experience led him to embark on a visit to St. Jude as a Fulbright Visiting Scientist, a prestigious fellowship awarded to select scholars by the U.S. State Department. Jai arrived on campus in April and was hosted by CBT through January 2022. While at St. Jude, he was focused on developing complex molecules that aid in drug development. New discussions led to synergistic interactions between scientists at St. Jude and faculty at IICB and other scientific organizations in India. During his time at St. Jude, Jai laid the groundwork that will lead to future collaborations between St. Jude and the Council of Scientific & Industrial Research (CSIR), the largest research and development organization of the Government of India. Throughout his time at CBT, Jai fostered collaboration, innovation, and an all-around good time in the community. We wish him well as he returns to India and consider him a life-long member of the CBT community.

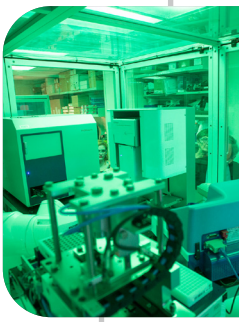


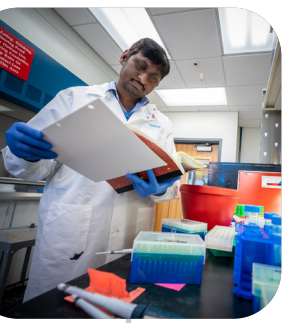








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