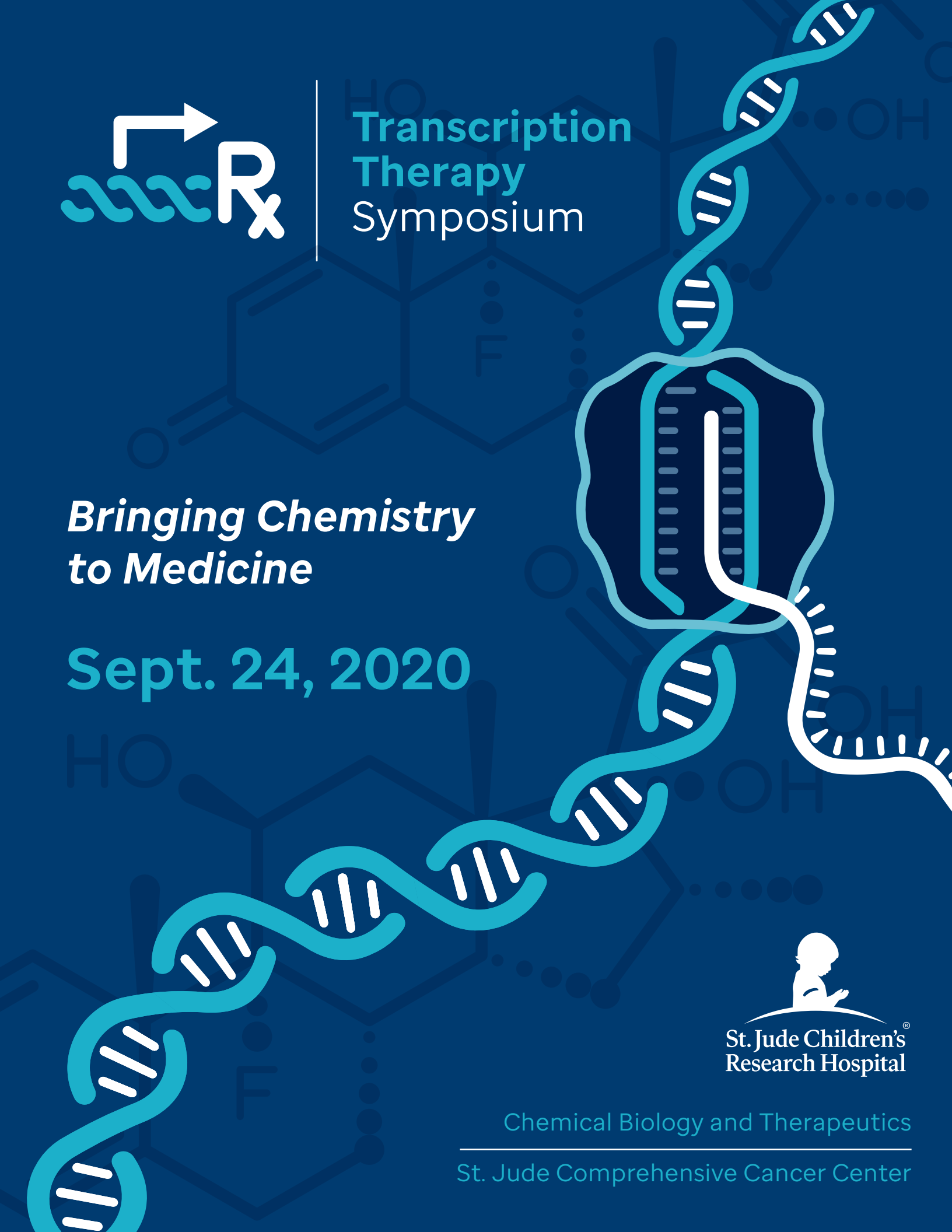
Transcription Therapy Symposium

Bringing Chemistry to Medicine

Sept. 24, 2020



St. Jude Children's Research Hospital®

Chemical Biology and Therapeutics

St. Jude Comprehensive Cancer Center

Transcription Therapy:
Bringing Chemistry to Medicine

Disruption of chromatin, epigenetic states and transcriptional regulation can lead to disease, including pediatric cancers. As our understanding of transcriptional regulation grows, so does our ability to design molecules that target these processes and create innovative transcription-targeted therapies.

The Transcription Therapy Symposium features thought leaders at the interface of chemical and biomedical sciences. We will explore novel chemical approaches to elucidate and regulate chromatin and epigenetic landscapes. Emerging targets for chemical intervention to remedy disease-associated gene regulation will be the focus of the panel discussions.

Welcome

Aseem Z. Ansari

St. Jude Children's Research Hospital

Chair, Chemical Biology & Therapeutics

R. J. Ulrich Endowed Chair

Charles W. M. Roberts

Executive Vice President

Director, Comprehensive Cancer Center

Director, Molecular Oncology Division

Opening Remarks

James R. Downing, MD

St. Jude Children's Research Hospital

President and Chief Executive Officer

Director, Molecular Pathology Laboratory

Donald Pinkel Chair of Childhood Cancer Treatment

St. Jude and Transcription Therapy Research:

While transcription therapy is still a nascent discipline, it is a growing strategic and scientific focus at St. Jude. The institution has a history of using small-molecule compounds to therapeutically target gene regulation. One of the hard-won successes in treating pediatric leukemia relies on targeting the glucocorticoid receptor, a transcription factor. The application of glucocorticoid receptor agonists into chemotherapy regimens for pediatric patients with acute lymphoblastic lymphoma (ALL) dramatically increased overall survival rates for newly diagnosed ALL to 94% at St. Jude. The breakdown of gene regulation is at the core of many pediatric diseases, but it is also a fundamental puzzle in biology that thought leaders at the interface of different fields of study are trying to solve.

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.

Schedule of Events: Session 1

TIME	EVENT
8:45 - 9:00 am	**Login**
9:00 - 9:05 am	**Charles Roberts** and **Aseem Ansari** Welcome
9:05 - 9:15 am	**James R. Downing, MD**, ***President and CEO of St. Jude Children's Research Hospital*** Opening Remarks
Session 1:	**Chromatin - Moderator: Charles Roberts**
9:15 - 9:40 am	**Charles Roberts** Chromatin Remodeler Mutations in Cancer: Mechanisms and Therapeutic Vulnerabilities
9:45 - 10:10 am	**Stephen Frye** Allosteric Antagonists of Methyl-lysine Reader Domain Interactions with DNA/RNA
10:15 - 10:30 am	**Break**
10:30 - 10:55 am	**Tom W. Muir** Painting Chromatin with Synthetic Protein Chemistry
11:00 - 11:25 am	**Joanna Wysocka** Making Faces: Transcriptional Enhancers and Emergence of Form and Function During Development and Evolution
11:30 - 12:00 pm	**Panel Discussion**
12:00 - 12:30 pm	**Break**

Schedule of Events: Session 2 and 3

TIME	EVENT
Session 2:	**New Concepts - Moderator: Aseem Ansari**
12:30 - 12:55 pm	**Rick Young** Nuclear Condensates in Gene Regulation, Disease Pathology and Drug Partitioning
1:00 - 1:15 pm	**Discussion**
Session 3:	**Transcription Factors - Moderator: Aseem Ansari**
1:15 - 1:40 pm	**Aseem Z. Ansari** Chemical Control of Gene Expression
1:45 - 2:10 pm	**Anna Mapp** Writing the Rules for Targeting Dynamic Transcriptional Coactivators
2:15 - 2:30 pm	**Break**
2:30 - 2:55 pm	**Paramjit Bobby Arora** Systematic Targeting of Transcription Factor-Coactivator Protein-Protein Interactions
3:00 - 3:25 pm	**Nathanael Gray** Developing the Next-Generation of Transcription-Targeting Therapeutics
3:30 - 4:00 pm	**Panel Discussion**
4:00 - 4:15 pm	**Aseem Z. Ansari** Concluding Remarks

Session 1: Chromatin

Charles W. M. Roberts

9:15 - 9:40 am

Chromatin Remodeler Mutations in Cancer: Mechanisms and Therapeutic Vulnerabilities

Abstract:
Research in the Roberts laboratory focuses on the SWI/SNF (BAF) chromatin remodeling complex. Perturbation of this complex has broad relevance to cancer as at least nine genes that encode SWI/SNF subunits collectively mutated in over 20% of all cancers. The lab studies both the mechanisms by which SWI/SNF normally regulates chromatin structure and cell fate, and the mechanisms by which mutation of the complex drives cancer formation. Recent data on our insights into the normal function of SWI/SNF complexes, the mechanisms by which mutation of the complexes drive cancer formation, and potential therapeutic vulnerabilities created by mutation of the complex will be presented.

About the Speaker:
Charles W. M. Roberts, M.D., Ph.D., is a leader in the field of cancer epigenetics. His research has provided new insights into the central role of chromatin remodeling perturbations in cancer, discoveries that have been translated into investigational therapies for both pediatric and adult cancer patients. Roberts received his medical and doctoral degrees from Washington University School of Medicine in St. Louis, Missouri. He completed his pediatric residency and pediatric hematology/oncology fellowship at Boston Children's Hospital/Dana-Farber Cancer Institute. Roberts has been elected to the Society for Pediatric Research, American Society of Clinical Investigation and American Pediatric Society.

Session 1: Chromatin

Stephen V. Fyre

9:45 - 10:10 am

Allosteric Antagonists of Methyl-lysine Reader Domain Interactions with DNA/RNA

Abstract:
Polycomb-directed repression of gene expression is frequently misregulated in human diseases. A quantitative and target-specific cellular assay was utilized to discover the first potent positive allosteric modulator (PAM), UNC4976, of nucleic acid binding by CBX7, a chromodomain methyl-lysine reader of Polycomb repressive complex 1. The PAM activity of UNC4976 resulted in enhanced efficacy across three orthogonal cellular assays by simultaneously antagonizing H3K27me3-specific recruitment of CBX7 to target genes while increasing non-specific binding to DNA and RNA. PAM activity thereby reequilibrates PRC1 away from H3K27me3 target regions. Together, our discovery and characterization of UNC4976 not only revealed the most cellularly potent PRC1-specific chemical probe to date, but also uncovers a potential mechanism of Polycomb regulation with implications for non-histone lysine methylated interaction partners. Extension of allosteric inhibitor discovery to other methyl-lysine reader domains will also be discussed.

About the Speaker:
Stephen Frye, Ph.D. is currently a Fred Eshelman Distinguished Professor and the Director of the Center for Integrative Chemical Biology and Drug Discovery (CICBDD) at the University of North Carolina at Chapel Hill (UNC). He is also co-director of the Molecular Therapeutics program in the Lineberger Comprehensive Cancer Center. Prior to joining UNC to create the CICBDD in 2007, Dr. Frye was the worldwide vice president of Discovery Medicinal Chemistry (DMC) at GlaxoSmithKline (GSK). Dr. Frye led DMC for seven years, overseeing five departments and more than 200 chemists in the U.S. and U.K., developing global protein target-class chemical science for GSK. As director of the Center for Integrative Chemical Biology and Drug Discovery at UNC, Dr. Frye plays a key role in translational research through collaborative drug discovery projects with other UNC faculty. The Center has initiated a program in the area of chemical biology of chromatin regulation with an emphasis on protein-protein interactions dependent upon lysine methylation. The first investigational new drug approved compound discovered in the Center, is now progressing through multiple clinical trials.

Session 1: Chromatin

Tom W. Muir

10:30 - 10:55 am

Painting Chromatin with Novel Protein Chemistries

Abstract:
Understanding protein function is at the heart of experimental biology. Perhaps one of the grandest contemporary challenges in this area is to catalog and functionally characterize protein post-translational modifications (PTMs). Modern analytical techniques reveal that most, if not all, proteins are modified at some point; it is nature's way of imposing functional diversity on a polypeptide chain. Understanding the structural and functional consequences of all these PTMs is a devilishly difficult problem. While standard molecular biology methods are of limited utility in this regard, modern protein chemistry provides powerful methods that allow the detailed interrogation of protein PTMs. In this lecture, I will highlight how these tools can be used to probe a series of problems in chromatin biology. Particular emphasis will be given towards the development of methods for the preparation and analysis of large encoded libraries of modified chromatins, as well as technologies for customizing cellular chromatin in situ using chemistry.

About the Speaker:
Tom W. Muir received both his B.Sc. in Chemistry in 1989 and his Ph.D. in Chemistry in 1993 from the University of Edinburgh under the direction of Professor Robert Ramage. After his postdoctoral studies with Stephen B.H. Kent at The Scripps Research Institute, he joined the faculty of Rockefeller University in 1996, where he was the Richard E. Salomon Family Professor and Director of the Pels Center of Chemistry, Biochemistry and Structural Biology until 2011. Dr. Muir then joined the faculty of Princeton University as the Van Zandt Williams Jr. Class of '65 Professor of Chemistry. There, he currently serves as Chair of the Chemistry Department. He has published over 200 scientific articles in the area of chemical biology and is best known for developing methods for the preparation of proteins containing unnatural amino acids, post-translational modifications and spectroscopic probes. These approaches are now widely employed in academia and industry. His current interests lie in the area of epigenetics, where he tries to illuminate how chemical changes to chromatin drive different cellular phenotypes.

Session 1: Chromatin

Joanna Wysocka

11:00 - 11:25 am

Making Faces: Transcriptional Enhancers and Emergence of Form and Function During Development and Evolution

Abstract:
A class of cis-regulatory elements, called enhancers, plays a central role in orchestrating spatiotemporally precise gene expression programs during development. Our laboratory is interested in molecular mechanisms by which enhancers regulate expression of their target genes over large genomic distances. In addition, we are using facial progenitor cells, called Cranial Neural Crest Cells (CNCCs) as a paradigm to study how genetic information harbored by enhancers is decoded into a diversity of functions, behaviors and morphologies. I will discuss our latest work on how changes in enhancer sequence and function can lead to normal-range and disease-associated morphological variation of the human craniofacial form. I will illustrate how, despite redundancies in complex mammalian regulatory landscapes, even small alterations in gene expression caused by enhancer loss can lead to changes in morphology.

About the Speaker:
Joanna Wysocka, Ph.D. completed her doctoral work at the Cold Spring Harbor Laboratory with Dr. Winship Herr and, after graduating in 2003, postdoctoral training at the Rockefeller University with Dr. David Allis. Wysocka's research is focused on understanding gene regulatory mechanisms in human development, disease and evolution. Her lab is employing a broad combination of genomic, genetic, biochemical, biophysical, single-cell and embryological approaches in a number of cellular and organismal models to investigate functions of the non-coding parts of the genome, and to understand regulatory mechanisms underlying stem cell function, cellular plasticity, and differentiation. She is investigating how quantitative changes in gene expression dictate differences in human traits, and also studies craniofacial development and variation. Wysocka is a recipient of numerous awards, including the Searle Scholar Award, W.M. Keck Foundation Distinguished Young Scholar Award, ISSCR Outstanding Young Investigator Award and Vilcek Prize for Creative Promise. She was elected to the American Academy of Arts and Sciences in 2018 and to EMBO in 2019.

Session 2: New Concepts

Rick Young

12:30 - 12:55 pm

Nuclear Condensates in Gene Regulation, Disease Pathology and Drug Partitioning

Abstract:
Recent studies have shown that many nuclear processes occur within biomolecular condensates. These condensates compartmentalize and concentrate the community of protein and RNA molecules involved in each process, typically at specific genomic loci, and may thus provide a special physicochemical environment for the process. I will discuss evidence that widely used anti-cancer drugs selectively partition into condensates, thereby altering their pharmacodynamic properties. This new understanding of chemical partitioning has implications for the development of new therapeutics for cancer and other diseases.

About the Speaker:
Richard Young, Ph.D. is a Professor at the Whitehead Institute and MIT. Dr. Young studies gene regulation in health and disease. He has served as an advisor to the World Health Organization, the National Institutes of Health and numerous scientific societies and journals. Young's honors include membership in the National Academy of Sciences, National Academy of Medicine, and *Scientific American* has recognized him as one of the top 50 leaders in science, technology and business. He has founded and advised companies in the biotechnology and pharmaceutical industry, and currently serves on the boards of Syros Pharmaceuticals, CAMP4 Therapeutics, Omega Therapeutics and Dewpoint Therapeutics. Young is also an aviator and holds a commercial pilot license.

Session 3: Transcription Factors

Aseem Z. Ansari

1:15 - 1:40 pm

Chemical Control of Gene Expression

Abstract:
How is genomic information utilized to give rise to distinct human cell types? Can we remedy dysfunctional transcriptional circuits in diseased cells with synthetic/chemical gene regulators? These questions guide our “discover by design” efforts to rationally design small molecules that perturb and thereby reveal gene regulatory networks that govern cell fate choices. Our breakthrough in creating synthetic transcription factors that overcome epigenetic silencing to restore expression of frataxin, fuels our efforts to develop “Transcription Therapeutics” to rectify other disease-causing malfunctions in gene regulation.

About the Speaker:
Aseem Z. Ansari is the Chair of Chemical Biology and Therapeutics at the St. Jude Children’s Research Hospital. Dr. Ansari pioneered the creation of synthetic transcription factors that control human stem cell fate choices and remedy the regulation of disease-associated gene networks. Aseem began his scientific career as a summer intern in the laboratory of Dr. Obaid Siddiqi at Tata Institute of Fundamental Research (TIFR) in Bombay. He obtained his Ph.D. at Northwestern University and completed his postdoctoral training as a Helen Hay Whitney Fellow at Harvard and MIT. Prior to joining St. Jude in 2019, Aseem was a professor at the University of Wisconsin-Madison and was the recipient of the NSF CAREER award, Keck Foundation Research Excellence award, Shaw scholar and Basil O’Connor scholar awards.

Session 3: Transcription Factors

Anna Mapp

1:45 - 2:10 pm

Writing the Rules for Targeting Dynamic Transcriptional Coactivators

Abstract:
Transcriptional coactivators and their partner transcription factors have been labeled as intrinsically disordered, fuzzy, and undruggable. We propose that the identification of conserved mechanisms of engagement between coactivators and their cognate activators should provide general principles for small-molecule modulator discovery. Towards that end, biophysical characterization of the structurally divergent coactivator Med25 reveals that it forms short-lived and dynamic complexes with three different transcriptional activators and that conformational shifts are mediated by a flexible substructure of two dynamical helices and flanking loops. Analogous substructures are found across eukaryotic coactivators. Furthermore, targeting one of the flexible structures with a small molecule modulates Med25-activator complexes. Thus, the two conclusions of the work are actionable for the discovery of small-molecule modulators of this functionally important protein class.

About the Speaker:
Anna K. Mapp received an A.B. in Chemistry from Bryn Mawr College and a Ph.D. in Organic Chemistry from University of California, Berkeley. Following a postdoctoral fellowship at Caltech, she began her independent career at the University of Michigan. Mapp's research interests center around the conformationally dynamic protein complexes that are central to gene activation. More specifically, her group uses multidisciplinary strategies to define the molecular recognition framework of transcriptional coactivator-transcription factor complexes and to use the framework to target the complexes for therapeutic purposes. She has received a number of awards for her work, including election to the American Academy of Arts & Sciences, the Harold R. Johnson Diversity Service Award, and the Emil T. Kaiser Award. Outside of the University of Michigan Mapp serves as an Associate Editor of the journal ACS Chemical Biology, member of the Basic Science Council of the National Cancer Institute, member of the Scientific Advisory Board of the Max Planck Institute of Chemical Ecology and an organizer of PACIFICHEM 2021.

Session 3: Transcription Factors

Paramjit “Bobby” Arora

2:30 - 2:55 pm

Systematic Targeting of Transcription Factor-Coactivator Protein-Protein Interactions

Abstract:
We are pursuing a systematic approach to develop synthetic inhibitors of PPIs. Proteins often utilize small folded domains for recognizing other biomolecules. The basic hypothesis guiding our research is that by mimicking these domains, we can modulate the function of a particular protein with metabolically stable synthetic molecules. This presentation will discuss covalent constraints to stabilize protein domain mimics (PDMs) in isolated sequences. This talk will present the application of PDMs to develop ligands for protein-protein interaction modules of p300.

About the Speaker:
Paramjit Arora, Ph.D. is a professor of Chemistry at New York University. He obtained his B.S. in Chemistry from the University of California, Berkeley and received his Ph.D. in Chemistry from UC Irvine with James Nowick. He pursued a postdoctoral fellowship at the California Institute of Technology with Peter Dervan, Ph.D. before joining the faculty of New York University. His research group uses rational design to develop peptides and peptidomimetics to interrogate protein-protein interactions.

Session 3: Transcription Factors

Nathanael Gray

3:00 - 3:25 pm

Developing the Next-Generation of Transcription-Targeting Therapeutics

Abstract:
Finding pharmacological strategies to control gene expression has been a longstanding goal of drug discovery. To-date the greatest success has been achieved by targeting the nuclear hormone receptors (ER, AR, GR) which were amenable to conventional 'occupancy-based' drug development strategies. Less success has been achieved for direct targeting of transcription factors that serve as the master regulators of gene expression control. This is because these proteins often lack known enzymatic functions or binding pockets for conventional small molecules. The current wave of transcription targeting drugs focuses on targeting the factors that regulate chromatin through binding, introducing or removing post-translational modifications. This seminar will focus on our laboratory's effort to target the cyclin dependent kinases (CDKs) which is a 20-member family that exerts dominant control over all aspects of transcription and cell cycle control. I will also describe the development of proximity based therapeutics – typically bivalent molecules that hijack endogenous enzymatic functions to afford new forms of pharmacology including protein degradation and recruitment of kinases and phosphatases. Proximity-based therapeutics have the potential to transform our ability to manipulate transcription pharmacologically.

About the Speaker:
Nathanael Gray, Ph.D., is the Nancy-Lurie Marks Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School and the Dana-Farber Cancer Institute. He also leads the Dana-Farber Program in Chemical Biology. Dr. Gray's research centers on drug development and medicinal chemistry related to targeted therapies for cancer. Four drugs that he has had a hand in developing have already been approved the U.S. Food and Drug Administration or are currently in clinical trials. Before joining Harvard and Dana-Farber, Dr. Gray was director of the Genomics Institute of the Novartis Research Foundation. He earned his Ph.D. from the University of California, Berkeley.

Hosted by

St. Jude Comprehensive Cancer Center

The St. Jude Comprehensive Cancer Center, led by director Charles W.M. Roberts, MD, PhD, is the only NCI-designated Comprehensive Cancer Center devoted solely to children. To advance research, treatment, and cures for childhood cancer, the center provides an overarching strategic vision and scientific direction, a collaborative framework, state-of-the-art shared resources, and an administrative hub that supports its members in making scientific breakthroughs.

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.

Symposium Committee

Natalie Racine
CBT Manager of Operations

Carole Weaver, Ph.D.
Cancer Center Program Director

Anna Acerra
Manager of Digital Business

Elizabeth Whittington
Director of Digital Media

Erin Seidler
Senior Director of Public Relations

Special Thanks: **Josh Stokes and Madison Rice** for Symposia Visual Design

Thank you

Learn More:

St. Jude

CBT

Comprehensive Cancer Center