2021

Bringing Chemistry to Medicine

Symposium

July 22
Transcription Therapy

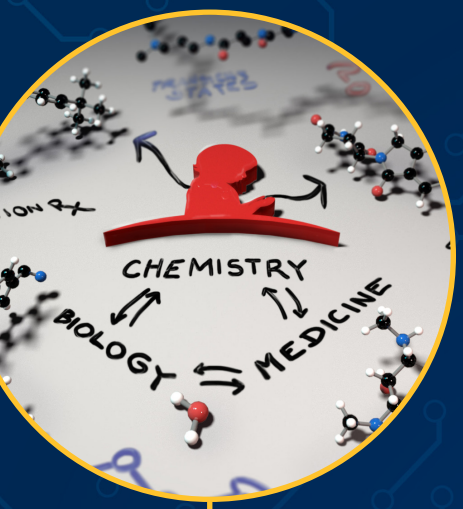
July 23
Frontiers in Chemical Biology

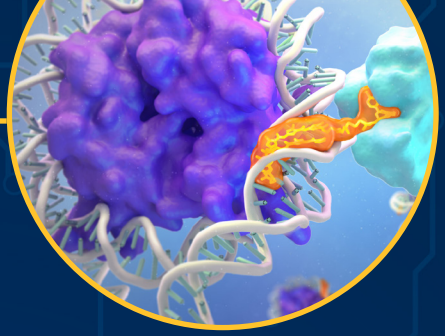
Hosted by:

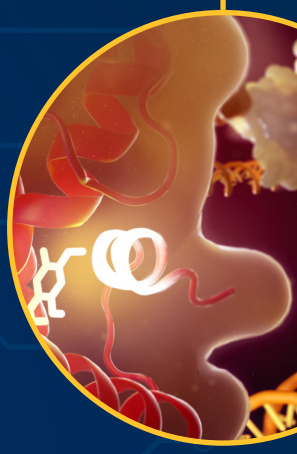
St. Jude Children's Research Hospital

Department of Chemical Biology and Therapeutics

St. Jude Comprehensive Cancer Center







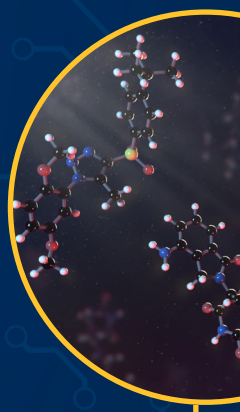
Bringing Chemistry to Medicine

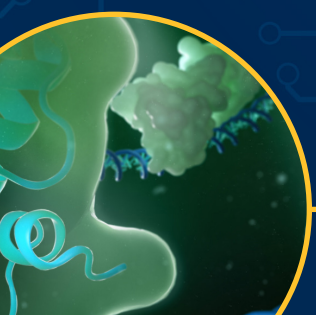
Virtual Symposium

Hosted by:
St. Jude Department of Chemical Biology and Therapeutics
St. Jude Comprehensive Cancer Center

The Bringing Chemistry to Medicine Symposium features thought leaders at the interface of chemical and biomedical sciences, working in areas spanning therapeutic regulation of transcription and chromatin, computational biology, and chemical biology.

Transcription Therapy: *Thursday, July 22*
and
Frontiers in Chemical Biology: *Friday, July 23*





St. Jude Children's® Research Hospital
Finding cures. Saving children.

Hosted by

Chemical Biology and Therapeutics

The Chemical Biology and Therapeutics Department at St. Jude, led by chair Aseem Ansari, formulates innovative chemical and chemoinformatic solutions to resolve salient problems in biology and medicine. Fundamental research programs to uncover underlying biological processes are complemented by translational centers that house chemical synthesis, screening, and computational capabilities that mirror cutting-edge biotech/pharma operations, resources rarely accessible at academic institutions. The expertise and resources of CBT are leveraged across the institution, making it a highly dynamic and diverse collaborative hub at St. Jude. The scientific research arm of CBT is in an exciting growth phase; individuals with bold vision and demonstrated excellence in research at the interface of chemistry, biology, and medicine are encouraged to join the team.

St. Jude 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.

St. Jude Children's Research Hospital®
Finding cures. Saving children.

July 22: Transcription Therapy

9:00-9:15 AM CDT	**Opening Remarks** Charles W.M. Roberts, MD, PhD, Aseem Ansari, PhD	
9:15-9:45	**Suzanne J. Baker, PhD** Intro: Jamy C. Peng, PhD	**Histone Mutations and Disrupted Development in Pediatric High-Grade Glioma**
9:45-10:15	**Patrick Cramer, PhD** Intro: Mario Halic, PhD Silvija Bilokapic, PhD	**Recent Insights into Chromatin Transcription**
10:15-10:30	**Break**	
10:30-11:00	**Jonathan D. Licht, MD** Intro: John Crispino, PhD, MBA	**NSD2 in Lymphoid Malignancy**
11:00-11:30	**Cigall Kadoch, PhD** Intro: Hai Dao, PhD	**Structure and Function of Mammalian SWI/SNF Chromatin Remodeling Complexes in Human Cancer**
11:30-12:00	**Panel**	
12:00-12:30	**Lunch**	
12:30-1:00	**James E. Bradner, MD** Intro: Adam D. Durbin, MD, PhD	**Chemical Control of Gene Expression**
1:00-1:15	**Discussion**	
1:15-1:45	**William G. Kaelin Jr, MD** Intro: Anand Patel, MD, PhD	**Three Possible Paths to Targeting Undruggable Transcription Factors**
1:45-2:15	**Andrea Califano, PhD** Intro: Jiyang Yu, PhD	**Elucidation and Pharmacologic Targeting of Single Cell State Maintenance Mechanisms**
2:15-2:30	**Break**	
2:30-3:00	**Anjana Rao, PhD** Intro: Benjamin A. Youngblood, PhD	**Transcriptional Networks in Tumor-infiltrating T cells**
3:00-3:30	**Mitchell A. Lazar, MD, PhD** Intro: Daniel Savic, PhD	**Personalization of Transcription Therapy With Drugs Targeting Nuclear Receptors**
3:30-4:00	**Panel**	
4:00-4:15	**Closing Remarks** Charles W.M. Roberts, MD, PhD, Aseem Ansari, PhD	

July 23: Frontiers in Chemical Biology

9:00-9:15 AM CDT	**Opening Remarks** Aseem Ansari, PhD, Anang Shelat, PhD	
9:15-9:45	**Pedro R. Cutillas, PhD** Intro: Tommaso Cupido, PhD	**Rationalizing Anti-Cancer Drug Responses Using Proteomics and Machine Learning: Towards Next Generation Precision Medicine**
9:50-10:15	**Francesca Ciccarelli, PhD** Intro: Tommaso Cupido, PhD	**Predictors of Response to Cancer Immunotherapy: Beyond Tumour Mutational Burden**
10:15-10:30	**Break**	
10:30-11:00	**Debora S. Marks, PhD** Intro: Tommaso Cupido, PhD	**Prediction and Design of Proteins with Neural Machines**
11:00-11:30	**Tobin R. Sosnick, PhD** Intro: Marcus Fischer, PhD	**Prediction of a Protein's Free Energy Surface with Validation Using Hydrogen/Deuterium Exchange**
11:30-11:45	**Break**	
11:45-12:15	**Prof. Dame Janet Thornton** Intro: Marcus Fischer, PhD	**Computational Enzymology: The Structure, Function and Evolution of Enzymes**
12:15-12:45	**M. Madan Babu, PhD, FRSC** Intro: Marcus Fischer, PhD	**Variation in GPCR Signaling: Implications for Drug Discovery**
12:45-1:15	**Panel**	
1:15-1:45	**Break**	
1:45-2:15	**Craig W. Lindsley, PhD** Intro: Taosheng Chen, PhD, PMP	**Discovery and Development of GPCR Allosteric Ligands: From Concept to Clinic**
2:15-2:45	**Marvin J. Miller, PhD** Intro: Stephanie M. Reeve, PhD	**Design, Syntheses and Studies of New Antibiotics**
2:45-3:00	**Break**	
3:00-3:30	**Craig M. Crews, PhD** Intro: Zoran Rankovic, PhD	**PROTAC-mediated Protein Degradation: A New Therapeutic Modality**
3:30-4:00	**Panel**	
4:00-4:15	**Closing Remarks** Aseem Ansari, PhD	

Bringing Chemistry to Medicine Symposium

July 22, 2021

Transcription Therapy

Chemical Biology and Therapeutics

St. Jude Comprehensive Cancer Center

St. Jude Children's Research Hospital®

Transcription Therapy at St. Jude

We have spent decades researching pediatric cancers and catastrophic diseases. This work led us to a growing understanding of the molecular and genetic mechanisms that underlie these diseases. We now know that anomalous epigenetic changes, disruption in chromatin states and errors in transcriptional regulation can lead to certain pediatric cancers and other catastrophic diseases.

At St. Jude, a large and diverse group of researchers and clinicians is driving efforts to target gene regulation and grow our understanding of the mechanisms behind pediatric cancer and other diseases. From chemists looking at drugs and making molecules to clinicians treating children every day, research into transcription therapeutics includes a wide range of departments and divisions across the institution and our Comprehensive Cancer Center. Working together allows us to examine how mechanistic insight can be tied to clinical outcomes and how clinical indications connect back to our understanding of the disease.

The Symposium

Our work and commitment is not limited to within the walls of St. Jude. We also have crucial collaborations with leading scientific and clinical institutions around the world. A key objective of the Transcription Therapy focus in this symposium is to engage the global scientific community in envisioning new solutions to remedy disease-causing malfunctions in gene transcription.

Building on our first-in-kind 2020 symposium on this topic, day 1 of this event focuses on the theme of Transcription Therapy, bringing together leaders in chemical and biomedical sciences to learn and share advances in transcription therapies for a range of diseases. We are pleased to host the newest transcription discoveries of 2021 from a group of world-renowned researchers, whose work is changing the face of medicine.

Comprehensive Cancer Center Research Programs

The Cancer Center supports five major interdisciplinary research programs that are organized with the specific intent of translating basic science discoveries into curative therapies for children with cancer, while minimizing long-term side effects.

1

Cancer Biology Program

Leads integrated and multidisciplinary efforts to define pathways related to cancer and its control, identify driver mutations and genetic anomalies as new targets for translation into clinical trials, and advance our understanding of the cancer microenvironment as a route to therapy.

2

Neurobiology & Brain Tumor Program

Aims to improve survival and morbidity for children with brain tumors by developing effective, relatively non-toxic therapies through a better understanding of disease pathogenesis.

3

Developmental Biology & Solid Tumor Program

Aims to improve the survival and quality of life of children with solid tumors by integrating basic, translational and clinical research.

4

Hematological Malignancies Program

Aims to improve the cure rates for childhood leukemias and lymphomas, while minimizing treatment-related adverse effects.

5

Cancer Control & Survivorship Program

Conducts clinical, genetic and observational research, translates findings into effective strategies to reduce treatment-related complications, and improves the quality of life of childhood cancer survivors.

Opening Remarks

Aseem Z. Ansari, PhD
Chair, Chemical Biology & Therapeutics
R. J. Ulrich Endowed Chair

Charles W. M. Roberts, MD, PhD
Executive Vice President
Director, Comprehensive Cancer Center
Director, Molecular Oncology Division

9:15 - 9:45 AM

Suzanne J. Baker

Director, Brain Tumor Research Division, St. Jude Children's Research Hospital
Associate Director, Basic Research, St. Jude Comprehensive Cancer Center

Histone Mutations and Disrupted Development in Pediatric High-Grade Glioma

Histone H3 mutations are a unifying molecular hallmark of pediatric high-grade glioma, highlighting a unique pathogenesis of this deadly disease in children compared to the more common glioblastomas arising in older adults. There is an intimate association between specific mutations and spatiotemporal tumor incidence, with H3 K27M mutations occurring in 80% of diffuse glioma arising in midline structures such as the pons and thalamus, and H3 G34R/V mutations arising in more than 15% of high-grade gliomas arising in the cortex of older adolescents and young adults. I will discuss our studies to investigate the contribution of these oncogenic histone mutations to disrupted transcription regulation, aberrant development and tumorigenesis.

About the Speaker

Suzanne J. Baker, PhD completed her doctoral training with Bert Vogelstein at Johns Hopkins University and postdoctoral training with Dr. Tom Curran at the Roche Institute of Molecular Biology. She is currently the Associate Director for Basic Research and Co-Leader of the Neurobiology and Brain Tumor Program at the St. Jude Children's Research Hospital Comprehensive Cancer Center, and the Associate Dean of the PhD program in the St. Jude Graduate School of Biomedical Sciences. Baker is recognized for her work on the molecular etiology of cancer and in vivo functional studies. She was the first to identify *TP53* mutations in human cancer as a graduate student and has focused her career on understanding how cancer-associated mutations drive disease pathogenesis. Her current work centers on the molecular mechanisms driving pediatric gliomas. She co-discovered the first histone mutations in human cancer, illuminating critical connections between development, epigenetics and cancer, and her laboratory is directed towards elucidating the underlying molecular, cellular, genetic and developmental mechanisms driving high-grade gliomas.

9:45 - 10:15 AM

Patrick Cramer

Director, Department of Molecular Biology
Max Planck Institute for Biophysical Chemistry

Recent Insights into Chromatin Transcription

Our laboratory combines structural biology with functional genomics to uncover the molecular mechanisms that underlie gene transcription and its regulation in eukaryotic cells. Recent work includes the high-resolution structure of the human transcription initiation complex containing RNA polymerase II (Pol II) and the cofactor Mediator, of Pol II elongation complexes in paused and active states, and of a first Pol II complex with a part of the spliceosome, U1 snRNP.
We have recently also shown how various accessory factors assist Pol II to pass through nucleosome for chromatin transcription. In my presentation, I will focus on the most recent work from the laboratory on Pol II transcription but will also briefly discuss our new insights into targeting the SARS-CoV-2 polymerase with coronavirus antivirals.

About the Speaker

Patrick Cramer, PhD, studied chemistry at the Universities of Stuttgart and Heidelberg (Germany) from 1989 until 1995. He completed a part of his studies as an ERASMUS scholar at the University of Bristol in the United Kingdom. As a research student, he also worked in the lab of Sir Alan Fersht in Cambridge, UK at the MRC Laboratory for Molecular Biology. From 1995 until 1998, he worked as a PhD student in laboratory of Christoph W. Müller at the European Molecular Biology Laboratory in Grenoble, France. He obtained his PhD in natural sciences from the University of Heidelberg in 1998. From 1999 until 2001, Cramer worked as a postdoctoral researcher and fellow of the German Research Foundation in the laboratory of the later Nobel Laureate Roger D. Kornberg at Stanford University, USA. In 2001, Cramer returned to Germany, where he obtained a tenure-track professorship for biochemistry at the Gene Center of Ludwig-Maximilians University Munich. Cramer headed the Gene Center from 2004 until 2013. He also served as Dean of the School of Chemistry and Pharmacy from 2007 to 2009, and as Director of the Department of Biochemistry from 2010 to 2013. Cramer also was a member of the University Research Board from 2007 to 2013 and speaker of the research network grant SFB464 of the German Research Council. On 1 January 2014, Cramer was appointed Director at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. He is a member of the Editorial Board for *Cell*.

10:30 - 11:00 AM

Jonathan D. Licht

Director, University of Florida Health Cancer Center
Marshall E. Rinker, Sr. Foundation and David B. and Leighan R. Rinker Chair

NSD2 in Lymphoid Malignancy

Pediatric ALL patients, particularly those in relapse, can harbor a specific point mutation (E1099K) in NSD2 (nuclear receptor binding SET domain protein 2) gene, also known as MMSET or WHSC1, which encodes a histone methyl transferase specific for H3K36me2. To understand the biological processes mediated by mutant NSD2, we used CRISPR-Cas9 gene editing to disrupt the NSD2E1099K mutant allele in B-ALL cell lines (RCH-ACV and SEM) and T-ALL cell line (RPMI-8402) or inserted the E1099K mutation into NSD2WT T-ALL cell line (CEM) and B-ALL cell line (697). Cell lines in which the NSD2E1099K mutant allele is present display increased global levels of H3K36me2 and decreased H3K27me3. NSD2E1099K cells demonstrate enhanced cell growth, colony formation and migration. NSD2E1099K mutant cell lines assayed by RNA-Seq exhibit an aberrant gene signature, mostly representing gene activation, with activation of signaling pathways, genes implicated in the epithelial mesenchymal transition and prominent expression of neural genes not generally found in hematopoietic tissues. Accordingly, NSD2E1099K cell lines showed prominent tropism to the central neural system in xenografts. Given GC resistance is a recurrent cause of relapsed refractory ALL, and EZH2 inhibitors can increase efficacy of GC in non NSD2 mutant ALL cells and other lymphoid malignancies, we propose that EZH2 inhibitors may be included in therapies for ALL as a bridge to CAR T cell or stem cell transplantation.

About the Speaker

Jonathan D. Licht, MD, is the Director of the University of Florida Health Cancer Center, holding the Marshall E. Rinker, Sr. Foundation and David B. and Leighan R. Rinker Chair. Licht's laboratory studies aberrant gene regulation. NCI funded for nearly 30 years, Licht is also Principal Investigator of a Leukemia and Lymphoma Society Specialized Center. For 10 years, Licht served as Senior Editor of *Clinical Cancer Research* and is currently an Associate Editor of *Oncogene* and *Clinical Epigenetics* and serves on the editorial boards of *Cancer Discovery, Cancer Blood Discovery, Cancer Research* and *Clinical Cancer Research.* Licht is a past councilor of the American Society of Hematology and co-led the 2017 American Society of Hematology/ European Hematology Association Translational Research Training program. Licht currently serves as chair of the Taskforce for Hematological Malignancies of the American Association for Cancer Research, serves on the Medical/Scientific Board of the Leukemia and Lymphoma Society and recently completed service as chair of the NIH Mechanisms of Cancer Therpeutics-1 Study Section. Licht has published over 200 original articles, reviews and book chapters. Licht has mentored over 40 graduate students, postdoctoral fellows and 20 faculty members.

11:00 - 11:30 AM

Cigall Kadoch

Associate Professor, Pediatric Oncology at the Dana-Farber Cancer Institute
Affiliate Faculty, Biological Chemistry and Molecular Biology at Harvard Medical School
Institute Member and Epigenomics Program Co-Director, Broad Institute and Harvard

Structure and Function of Mammalian SWI/SNF Chromatin Remodeling Complexes in Human Cancer

Genome-wide sequencing studies in human cancer have unmasked a striking frequency of mutations in the genes encoding subunits of the mammalian SWI/SNF (BAF) family of ATP-dependent chromatin remodeling complexes. Our laboratory uses biochemical, structural, and functional genomics-based approaches to study rare, genetically well-defined pediatric cancers including synovial sarcoma, Ewing sarcoma, malignant rhabdoid tumor and others, all of which involve BAF complex perturbations as critical drivers of their oncogenic programs. These studies have informed the mechanistic basis underlying BAF complex targeting and function and have provided new foundations for therapeutic development.

About the Speaker

Cigall Kadoch, PhD, is an Associate Professor of Pediatric Oncology at the Dana-Farber Cancer Institute, Affiliate Faculty of Biological Chemistry and Molecular Biology at Harvard Medical School, and Institute Member and Epigenomics Program Co-Director at the Broad Institute of MIT and Harvard. She established her independent laboratory in 2014, at age 28, one of the youngest scientists ever appointed to the Harvard Medical School faculty, immediately following completion of her PhD studies in cancer biology at Stanford University working with developmental biologist Gerald Crabtree. She has quickly become a leading expert in chromatin and gene regulation and is internationally recognized for her groundbreaking studies in these areas. Specifically, her laboratory studies the structure and function of chromatin remodeling complexes such as the mammalian SWI/SNF (or BAF) complex, with emphasis on defining the mechanisms underlying cancer-specific perturbations. Kadoch has received numerous prestigious awards and research grants to support her academic laboratory at Harvard, including the NIH Director's New Innovator Award, the Pew Scholar Award, the American Cancer Society Research Scholar Award, and, most recently, the American Association for the Advancement of Science (AAAS) Martin and Rose Wachtel Cancer Research Prize. Additionally, she was named to the Forbes 30 Under 30 list, MIT Technology Review 35 Innovators Under 35, Popular Science Brilliant 10, and Business Insider Top 30 Young Leaders in Biopharma.

12:30 - 1:00 PM

James E. Bradner

President of the Novartis Institutes for Biomedical Research (NIBR)

Chemical Control of Gene Expression

Disease biology research, on occasion, presents clarified opportunities for targeted therapeutic intervention. Regrettably, the discrete biomolecular target or target pathway is equally often just beyond the conceptual reach of traditional therapeutic modalities. The lowest hanging fruit (e.g. kinases, circulating proteins) is rapidly collected in a competitive race to potency, selectivity, and index clinical proof-of-concept; then this research is systematically reconsidered by a commodity market of thinly differentiated fast-followers. Left behind are a growing number of highly compelling, albeit difficult, validated targets, that await a conceptual reconsideration and generational advance in the science of therapeutics. Gene control factors are a prominent, structurally diverse functional class of proteins that are commonly linked to aberrant transcriptional signaling in disease biology, yet are perceived as intractable therapeutic targets. To organize around innovation in drugging transcription, we have created a new unit at the Novartis Institutes for Biomedical Research – Chemical Biology & Therapeutics. Our brand of chemical biology is unapologetically translational, seeing no barrier to atomically resolved mechanistic insights in the present study of human biology. This unit benefits from a legacy of contribution internally at NIBR and GNF in chemical genetics, allostery and modular therapeutic design, and the creativity of chemical biologists externally. In this seminar, I hope to share insights from our experience developing inhibitors of chromatin-associated complexes, and therapeutic modalities capable of approaching transcription factors. This talk will highlight progress in allostery, molecular machines, bifunctional protein degraders, molecular glues, covalent chemoproteomics and sequence-specific targeting of RNA by small molecules.

About the Speaker

James (Jay) Bradner, MD joined Novartis on January 1, 2016 and became President of the Novartis Institutes for Biomedical Research (NIBR) on March 1, 2016. He is a member of the Executive Committee of Novartis. Prior to joining Novartis, Bradner was on the faculty of Harvard Medical School in the Department of Medical Oncology at the Dana-Farber Cancer Institute from 2005 through 2015. Bradner is a co-founder of five biotechnology companies and has authored more than 250 scientific publications and 50 US patent applications. Bradner is a graduate of Harvard University and the University of Chicago Medical School. He completed his residency in medicine at Brigham and Women's Hospital and his fellowship in medical oncology and hematology at the Dana-Farber Cancer Institute. He has been honored with many awards and was elected into the American Society for Clinical Investigation in 2011 and the Alpha Omega Alpha Honor Medical Society in 2013.

1:15 - 1:45 PM

William G. Kaelin Jr.

Professor, Medicine, Harvard Medical School and Dana-Farber Cancer Institute
Senior Physician, Medicine, Brigham And Women's Hospital
Howard Hughes Medical Institute

Three Possible Paths to Targeting Undruggable Transcription Factors

Many transcription factors have been linked to various human diseases, including cancer. Examples of cancer-relevant transcription factors include c-Myc and b-catenin. Unfortunately, transcription factors, other than the steroid hormone receptors, are classically viewed to be "undruggable." In my talk, I will discuss several strategies for targeting undruggable transcription factors, including use of allosteric inhibitors, small molecule degraders, and drugs based on synthetic lethal relationships. In particular, I will present screening methodologies we have developed to facilitate the identification of degraders, as well as synthetic lethal targets.

About the Speaker

William G. Kaelin Jr, MD is a professor of medicine at Harvard University and the Dana-Farber Cancer Institute (DFCI). His laboratory studies tumor suppressor proteins. In 2016, Kaelin received the Albert Lasker Award for Basic Medical Research and the AACR Princess Takamatsu Award. He won the Nobel Prize in Physiology or Medicine in 2019 along with Peter J. Ratcliffe and Gregg L. Semenza. Kaelin earned his bachelor's degree in mathematics and chemistry at Duke University, and stayed to attain an MD, graduating in 1982. He did his residency in internal medicine at Johns Hopkins School of Medicine and his fellowship in oncology at DFCI. After deciding as an undergraduate that research was not a strength of his, he did research in the lab of David Livingston, where he found success in the study of retinoblastoma. In 1992, he set up his own lab at DFCI down the hall from Livingston's where he investigated hereditary forms of cancer such as von Hippel–Lindau disease. He became a professor at Harvard Medical School in 2002. He became Assistant Director of Basic Science at the Dana-Farber/Harvard Cancer Center in 2008. His work has been funded by the National Institutes of Health, American Cancer Society, Doris Duke Charitable Foundation and others. He serves as Vice-Chair of Scientific Programs on the Damon Runyon Cancer Research Foundation Board of Directors, chair of the Damon Runyon Physician-Scientist Training Award selection committee, member of the board of directors at Eli Lilly, and member of the Stand Up to Cancer scientific advisory committee.

1:45 - 2:15 PM

Andrea Califano

Chair, Department of Systems Biology
Director, JP Sulzberger Columbia Genome Center
Columbia University

Elucidation and Pharmacologic Targeting of Single Cell State Maintenance Mechanisms

We have developed network-based methodologies for the systematic identification, validation and pharmacological targeting of a new class of therapeutic targets. These targets comprise Master Regulator proteins, whose concerted aberrant activity within tightly regulated modules (tumor checkpoints) is responsible for the mechanistic implementation and maintenance of specific tumor cell states. By leveraging these methodologies, we have developed NY CLIA certified tests (OncoTreat and OncoTarget) that leverage large-scale drug-perturbation assays to systematically identify drugs and drug combinations whose mechanism of action is specifically effective in abrogating tumor checkpoint activity, on an individual patient basis. These tests have shown >80% success rate in PDX models from patients who had failed multiple standard of care therapies. In this talk, we will introduce these concepts and then demonstrate their application to elucidating drugs capable of targeting transcriptionally distinct tumor niches by single cell analysis. Specifically, we will discuss identification and in vivo validation of drugs targeting the stem-like progenitor niche of breast adenocarcinoma.

About the Speaker

Andrea Califano, PhD, is the Clyde and Helen Wu Professor of Chemical and Systems Biology at Columbia University Irving Medical Center, the Founding Chair of the Department of Systems Biology, and Director of the JP Sulzberger Columbia Genome Center. He also holds appointments in the Departments of Biochemistry & Molecular Biophysics, Biomedical Informatics, and Medicine. He was originally trained as a physicist and has applied physics-based approaches, including extensive use of information theory principles, to the reverse engineering and interrogation of gene regulatory networks to systematically and efficiently identify key tumor checkpoint modules, whose aberrant activity is necessary for tumor viability. This has resulted in several clinical trials, including a very innovative N-of-1 study for precision cancer medicine. Califano has received several awards and recognitions, including the NCI Outstanding Investigator Award; Fellow of the AAAS, and of the NY Academy of Medicine and Academy of Science; and Member of the National Academy of Medicine. He is also the co-founder of DarwinHealth Inc.

2:30 - 3:00 PM

Anjana Rao

Professor, La Jolla Institute for Immunology
Adjunct Professor, University of California San Diego Pharmacology

Transcriptional Networks in Tumor-infiltrating T-cells

The transcription factors NFAT and AP-1 (Fos-Jun) cooperate to promote the effector functions of T cells, but NFAT in the absence of AP-1 imposes a negative feedback program of T cell hyporesponsiveness ("exhaustion") by inducing and maintaining expression of the downstream transcription factors NR4A1/2/3 and TOX/TOX2. Two other transcription factors induced by TCR signaling, BATF and IRF4, also cooperate to counter T cell exhaustion in mouse tumor models. Overexpression of BATF in CD8+ T cells expressing a chimeric antigen receptor (CAR) promoted the survival and expansion of tumor-infiltrating CAR T cells, increased the production of effector cytokines, decreased the expression of inhibitory receptors and the exhaustion-associated transcription factor TOX, and supported the generation of long-lived memory T cells that controlled tumor recurrence. These responses were dependent on BATF-IRF interaction, since cells expressing a BATF mutant unable to interact with IRF4 did not survive in tumors and did not effectively delay tumor growth. BATF may improve the anti-tumor responses of CAR T cells by skewing their phenotypes and transcriptional profiles away from exhaustion and towards increased effector function.

About the Speaker

Anjana Rao, PhD, obtained her doctoral degree in biophysics from Harvard University and was a Professor at Harvard Medical School until 2011, when she moved to the La Jolla Institute and the University of California in San Diego (UCSD). Her research is focused on the regulation of gene expression, using immune cells, hematopoietic stem cells and embryonic stem cells as model systems. Her lab purified and molecularly characterized the calcium/calcineurin-regulated transcription factor NFAT, defined diverse transcriptional programs regulated by NFAT proteins in T cells, identified the pore subunit of the store-operated Ca2+ channel, ORAI1, and discovered that proteins of the TET family are enzymes that mediate DNA demethylation and regulate gene expression by oxidizing 5-methylcytosine. In recent studies, her lab has defined the role of NFAT and other transcription factors in anti-tumor responses and explored the roles of TET proteins and oxidized methylcytosines in the immune/hematopoietic systems and in embryonic development and oncogenesis. Rao is an elected member/fellow of the US National Academy of Sciences, the American Academy of Arts and Sciences and the American Association for the Advancement of Science.

3:00 - 3:30 PM

Mitchell A. Lazar

Willard and Rhoda Ware Professor in Diabetes and Metabolic Diseases
Director, University of Pennsylvania Institute for Diabetes, Obesity and Metabolism

Personalization of Transcription Therapy with Drugs Targeting Nuclear Receptors

Ligand-activated nuclear receptors (NRs) are the target of approximately 10-15% of prescribed drugs, including treatments for diabetes, osteoporosis, inflammation, and cancer. NRs control gene transcription by sequence-specific binding to non-protein-coding regions of the genome at regulatory sites called enhancers. We postulated that natural genetic variation at enhancers could lead to person-specific NR binding and function, that would alter the efficacy and/or undesired effects of drugs targeting NRs at the level of the individual. Applying a functional genomics approach including RNA-seq, ChIP-seq, and ChIA-PET techniques to human stem cell-derived adipocytes and hepatocytes, we uncovered single-nucleotide-polymorphisms (SNPs) that determine individual responses to thiazolidinediones, which target PPARg to treat diabetes, and corticosteroids, which target the glucocorticoid receptor and are used to reduce inflammation. This mechanism-based approach to finding functional SNPs has great potential for precision medicine and transcriptional therapies.

About the Speaker

Mitchell Lazar, PhD, received an BS degree in chemistry from MIT, and MD and PhD degrees from Stanford University. He trained in internal medicine at Brigham and Women's Hospital and in endocrinology at Massachusetts General Hospital, then joined the faculty of the University of Pennsylvania where he is the Willard and Rhoda Ware Professor in Diabetes and Metabolic Diseases. He served for many years as Chief of Endocrinology, Diabetes, and Metabolism, and is a Founding Director of Penn's Institute for Diabetes, Obesity, and Metabolism. Lazar's discoveries include the circadian nuclear receptor REV-ERB linking circadian rhythms and metabolism, the hormone resistin, and the importance of the nuclear receptor PPARg in adipocytes. He pioneered a modern approach to physiology that employs functional genomics and metabolic phenotyping to probe genetic, environmental, and circadian mechanisms contributing to diabetes and obesity. Lazar has given named lectures throughout the world and served as member of the NIDDK Council and numerous editorial and scientific advisory boards. He has been elected to the American Society for Clinical Investigation and the Association of American Physicians, where he served as President in 2021. He has received the Van Meter Award (American Thyroid Association), multiple awards from The Endocrine Society, the Stanley Korsmeyer Award (ASCI), the Luft Medal (Karolinska Institute), Transatlantic Award (UK Endocrine Society), and the Harrison Medal (Endocrine Society of Australia). Lazar is an elected member of the National Academy of Medicine, the American Academy of Arts and Sciences, and the National Academy of Sciences.

Bringing Chemistry to Medicine Symposium

July 23, 2021

Frontiers in Chemical Biology

Chemical Biology and Therapeutics

St. Jude Children's Research Hospital®

Chemical Biology and Therapeutics

The mission of St. Jude, to find cures and save children, imbues us with a profound sense of purpose and inspires beyond personal ambition. The institution provides agency, a collaborative ecosystem, and invaluable resources to tackle major scientific problems and make a difference.

Chemical Biology and Therapeutics (CBT) is an impressive department composed of two inter-related halves. One half of the department investigates biology with chemical approaches. The other is focused on developing novel therapeutic leads for future cures. In addition to nine academic laboratories, CBT houses seven collaborative centers that form the "Therapeutics" unit, with capabilities that are rarely accessible even at the best academic institutions in the world. A deep sense of camaraderie binds CBT's diverse community of students, staff and scientists. Over the past 2 years, the department has focused on amplifying its strengths and broadening its scope. The four pillars that guide our efforts are focusing on scientific excellence, faculty recruitment in emerging areas, funding for innovation, and improvement to form and function.

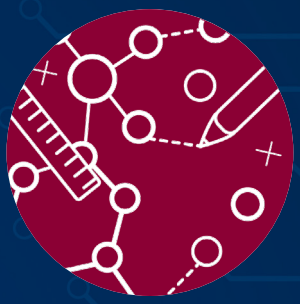
As we grow accustomed to the new normal, we remain focused on our defining goal: *to bring chemical concepts and tools to explore biology and create new medicines.* As we move forward, we will continue to grow, strive for excellence, and provide a fresh view of chemical biology to the global scientific community.

CBT Collaborative Centers

Leading state-of-the-art chemistry technologies, the CBT Collaborative Centers focus on research with investigators of St. Jude to further our understanding of the biological mechanisms in childhood diseases, with the goal of translating this knowledge into new therapeutic opportunities.

Chemical Biology Center:
applies advanced chemical biology methods to develop sophisticated chemical tools designed to map and interrogate disease-related biological pathways.

Analytical Technologies Center:
provides an extensive battery of assays designed to evaluate compound chemical, biophysical and ADME properties.



Medicinal Chemistry Center:
focuses on identifying and developing potent and selective small molecules to investigate disease-related biological targets in cells and in vivo preclinical models.

Project Management:
implements project management methodologies to generate knowledge, allow information capture, enhance communication, and provide faster process turnarounds to reduce project timelines for the translational drug discovery process.

Lead Discovery Informatics:
develops algorithms to model molecular interactions and predict drug efficacy, designs tools for visualizing and analyzing molecular properties and relationships, constructs data pipelines for lab automation and complex data analysis, and maintains laboratory information management systems.

High Throughput Biosciences:
aides in target identification and validation, assay development, high throughput screening, high content screening, laboratory automation, and management of scientific collaborations.

Compound Management:
aides in acquisition, registration, quality control, storage, retrieval, formatting and delivery of compounds to the researcher for biological screening and pre-clinical research with our small molecule compound library, using state-of-the-art automation and electronic data management systems.

9:15 - 9:45 AM

Pedro R. Cutillas

Professor, Cell Signalling and Proteomics
Centre for Cancer Genomics and Computational Biology
Barts Cancer Institute and Queen Mary University of London

Rationalizing Anti-Cancer Drug Responses Using Proteomics and Machine Learning: Towards Next Generation Precision Medicine

Kinase inhibitors, one of the major classes of new cancer drugs, are revolutionizing the way most tumor types are treated. However, not all cancer patients respond to kinase inhibitors to the same extent and most of those that initially respond eventually relapse. Current models used to rationalize responses, although successful in some settings, do not always explain such resistance phenotypes. Using the PI3K/Akt/mTOR pathway as a paradigm, our early work aimed to increase our understanding of why some tumors respond to targeted therapies while others are resistant to the same treatments. To this end, we first optimized technology for label-free phosphoproteomics and for deriving information on kinase activity from phosphoproteomics data. Using leukemia as a proof-of-concept, we found that the activities of pathways acting in parallel to PI3K determine whether or not leukemia cells may respond to PI3K inhibitors. As an extension of this work, we have recently found that specific combinations of pathway activities explain the efficacy of MEK and FLT3 inhibitors in leukemia cells. These data suggest that technology for measuring the signaling network as a whole (rather than just the pathway that is being targeted) may be able to predict clinical sensitivity to signaling inhibitors with greater accuracy than currently possible. More recently, we have applied this concept to systematically model and rationalize responses to drugs other than kinase inhibitors. This new approach, named Drug Ranking using Machine Learning, ranks drugs based on predicted efficacy to treat a given cancer patient.

About the Speaker

Pedro Cutillas, PhD, graduated with a doctoral degree in 2004 from the University College London. His studies, completed in the laboratories of Professor Mike Waterfield, Prof Rainer Cramer and Prof Al Burlingame, were on a project that investigated kidney physiology supervised by Prof Robert Unwin. Cutillas then completed postdoctoral training at the Ludwig Institute for Cancer Research (UCL branch). In 2007, Cutillas became a senior lecturer at the Centre for Cell Signaling in 2010. After a period in the MRC Clinical Sciences Centre (2012-2013), where he was Head of the Mass Spectrometry and Proteomics, Cutillas joined the Centre for Haemato-Oncology in 2013 where he led the Integrative Cell Signaling and Proteomics Group. In 2020, he was appointed as Professor of Cell signaling and Proteomics in the Centre for Cancer Genomics and Computational Biology. Cutillas holds Fellowships for the Turing Institute (the UK national institute for data science and AI), and from the Digital Environment Research Institute (QMUL, London). He is also academic co-founder and director of Kinomica Ltd, a spin-out company from his group.

9:45 - 10:15 AM

Francesca Ciccarelli

Professor of Cancer Genomics at King's College London
Group Leader at the Francis Crick Institute

Predictors of Response to Cancer Immunotherapy: Beyond Tumor Mutational Burden

Cancers with high mutation load are thought to respond better to cancer immunotherapy because their mutated proteins can be processed into neoantigens that stimulate the host immune system. However, there is large variability in the response rate even among patients with very unstable tumors, such as mismatch repair deficient colorectal cancers. We recently conducted an integrated study of the cancer tissue and associated tumor microenvironment from colorectal cancer patients treated with anti-PD1 immunotherapy. This enabled us to dissect the cellular and molecular determinants of response. This talk will summarize our findings and their implications for our understanding of the mechanisms of action of immunotherapy, leading to a better stratification of patients that will benefit from its use.

About the Speaker

Francesca Ciccarelli, PhD, is the Professor of Cancer Genomics at King's College London and Group Leader at the Francis Crick Institute. Ciccarelli graduated in Pharmaceutical chemistry at the University of Bologna and received a PhD in natural sciences from the University of Heidelberg where she worked under the supervision of Peer Bork at the European Molecular Biology Laboratory. There, she studied the evolution of genomes using comparative genomics and phylogenetics. In 2005, Ciccarelli started her independent research group at the European Institute of Oncology in Milan where she applied genomics and systems biology to study the evolution of gastrointestinal cancer. In 2014, she moved to King's College London and since 2017, her group is seconded to the Francis Crick Institute. Ciccarelli is co-lead of the patient stratification theme of the Cancer Research UK KHP Centre and of the cancer evolution theme of the Cancer Research UK (CRUK) City of London Cancer Centre. She works with a multidisciplinary team of biologists, mathematicians, oncologists, engineers and computer scientists who apply molecular genetics, data analysis and theoretical modelling to study cancer biology and evolution. The work in her lab is supported by Cancer Research UK, King's Health Partners and the European Union.

10:30 - 11:00 AM

Debora S. Marks

Associate Professor, Systems Biology
Harvard Medical School

Prediction and Design of Proteins with Neural Machines

What can we do with billions of genomes and immune repertoire sequences? We now have an amazing opportunity to develop machine learning methods that can exploit this enormous natural diversity to predict the effects of human genetic variation, to predict how viral genomes may evolve and to design biological sequences for therapeutics and biotechnology. I will demonstrate how unsupervised probabilistic generative modeling of sequences can give surprisingly direct answers to questions about 3D structures, dynamics, genetic variation and the design of biological molecules optimized for specific functions. I will end by introducing challenges for extending these methods to diverse applications to a broad range of biotechnology applications.

About the Speaker

Debora Marks, PhD, established her laboratory five years ago after a career in industry and more recent degrees in mathematics and computational biology, aiming to accelerate fundamental discoveries in biomedicine. Developing statistical methods including novel unsupervised machine learning, Marks' lab was able predict 3-dimensional protein structures from sequence alone, predict the fitness effects of human genetic variation, and make robust generative models for protein therapeutics, antibody design and deimmunization design. Most recently, she has extended these new tools to apply multimodal modeling of diverse biological and clinical data, including benchmarked approaches to combinations of RNA, protein and image data. Her mission is to develop AI for design of biological interventions for environment and human health (to save the world).

11:00 - 11:30 AM

Tobin R. Sosnick

Chair, Department of Biochemistry and Molecular Biology
University of Chicago

Prediction of a Protein's Free Energy Surface with Validation Using Hydrogen/Deuterium Exchange

Here we address a central challenge in protein biophysics, the de novo simulation of a protein's free energy surface including the identification of the rare, yet potentially biologically relevant, conformations. To this end, we have improved Upside, our near-atomic, extremely fast molecular dynamics algorithm that can cooperatively fold proteins with an accuracy comparable to all-atom methods. The reproduction of folding cooperativity in simulations requires a delicate balance between the energies of protein-protein and protein-solvent interactions. To achieve this balance, we introduce a new, dual-target training procedure that simultaneously teaches our energy function to have both stable native states and realistic denatured states. Validation is conducted using hydrogen-deuterium exchange. This sensitive, site-resolved technique provides a stringent test of a simulation's ability to reproduce both the structures and energies of the highest energy states. While our results are encouraging, this study underscores the significant challenges faced by simulations in generating accurate free energy surfaces.

About the Speaker

Tobin Sosnick, PhD, received his doctoral degree in low temperature physics from Harvard University in 1989. He transitioned to biophysics during his post-doctoral training with SW Englander (UPENN) and J Trewhella (Los Alamos National Lab) where he applied hydrogen exchange, NMR and small-angle X-ray scattering methods to study protein folding. Current research interests include experimental and computational studies of the folding, dynamics and assembly of soluble and membrane proteins; properties of denatured states; applications of hydrogen exchange to protein dynamics and folding using NMR and mass spectrometry; phase separation and stress response; ion channels and mechanobiology, and optogenetics. For the past 10 years, Sosnick has been the chair of the Department of Biochemistry and Molecular Biology. In addition, he is the co-founder of the Graduate Program in Biophysical Sciences, a unique dual-mentored graduate training program.

11:45 AM - 12:15 PM

Janet Thornton

Director Emeritus, European Bioinformatics Institute (EBI)
European Molecular Biology Laboratory (EMBL)

Computational Enzymology: The Structure, Function and Evolution of Enzymes

Many therapeutics target enzymes, modulating their functions in some way. We use computational approaches to improve our understanding of how enzymes work and how structures change during binding, catalysis or evolution. Almost all domains that perform catalysis have evolved to include many different family members that work on different substrates. To explore how these have evolved, we have generated family trees, showing the emergence of new specificities, and gaining a broad overview of enzyme evolution as we know it today. But we find that each family is different and careful analysis is required to understand individual mechanisms. These approaches will allow us to analyze complex enzyme families, their mechanisms and their evolution and maybe ultimately help in the design of new enzymes. In this talk I will focus on three practical topics: analysis of basic catalytic machinery in proteins from M-CSAusing sequences, a new way to estimate substrate transformations and find the most appropriate enzymes or pathways to transform a given substrate into a given product, and finally predicting enzyme mechanisms (with a reaction, 3D enzyme structure, algorithm and rules).

About the Speaker

Dame Janet Maureen Thornton is a senior scientist and director emeritus at the European Bioinformatics Institute, part of the European Molecular Biology Laboratory. She is one of the world's leading researchers in structural bioinformatics, using computational methods to understand protein structure and function. She was formerly director of the EBI from October 2001 to June 2015. After graduating in physics from the University of Nottingham, Thornton completed a master's degree in biophysics at King's College London, and a PhD in Biophysics at the National Institute for Medical Research in 1973. After her PhD, Thornton worked in molecular biophysics at the University of Oxford. In 1978, she returned to the National Institute for Medical Research, and following that took up to a Fellowship at Birkbeck College, part of the University of London. In 1990, she was appointed Professor and Director of the Biomolecular Structure and Modeling Unit in the Department of Biochemistry and Molecular Biology at University College London and later also was appointed to the Bernal Chair in the Crystallography Department at Birkbeck College. Thornton was Director of the European Bioinformatics Institute from 2001 to 2015. From 2008 to 2012, she co-ordinated the four-year preparatory phase of the European life sciences data infrastructure ELIXIR. Thornton was appointed Commander of the Order of the British Empire in 2000 and Dame Commander of the Order of the British Empire in the 2012 Birthday Honours for services to bioinformatics. The Times named Thornton number 86 of their "Eureka 100" British scientists in 2010. She was awarded the Suffrage Science award in 2011.

12:15 - 12:45 PM

M. Madan Babu

Faculty, St. Jude Structural Biology
Director, Center of Excellence for Data Driven Discovery
Endowed Chair in Biological Data Science

Variation in GPCR Signaling: Implications for Drug Discovery

G protein-coupled receptors (GPCRs) participate in diverse physiological processes, ranging from sensory responses such as vision, taste and smell to those regulating behavior, the immune and the cardiac system among others. The ~800 human GPCRs sense diverse signaling molecules such as hormones and neurotransmitters to allosterically activate the associated G proteins, which in turn regulate diverse intracellular signaling pathways. In this manner, GPCRs regulate virtually every aspect of human physiology. GPCRs are the targets of over one-third of all prescribed human drugs. In this presentation, I will first discuss how one could leverage data from diverse species to infer selectivity determinants of GPCR-G protein binding, which is critical to elicit the right intracellular response. Then, I will cover how one could utilize data on completely sequenced genomes of over 60,000 individuals from the human population to gain insights into natural receptor variation, which can result in variable drug response. Finally, I will present our recent work studying transcriptome data from over 30 different tissues in humans. I will conclude by discussing how understanding variation at these different dimensions (across different species, among different individuals of a species, and between tissues of a species) can provide a rich source of new hypotheses with implications for personalized medicine, drug development and understanding basic receptor biology.

About the Speaker

M. Madan Babu, PhD, is the Endowed Chair of Biological Data Science in the Department of Structural Biology at St Jude Children's Research Hospital. He is the Director of the Center of Excellence for Data Driven Discovery. Before joining St. Jude, Babu was a Programme Leader at the MRC Laboratory of Molecular Biology in Cambridge, UK (2006-2020). Babu's research group develops data science approaches to make biological discoveries with a particular emphasis on understanding how the precise structure and intrinsically disordered regions of proteins contribute to cellular function. His interests and publications span diverse areas in life sciences relevant to human diseases and medicine. The work from his group has been recognized with national and international awards including the Blavatnik Award for his work elucidating the functions of key proteins in the human genome (2018). Recently, he was awarded the 2019 EMBO Gold Medal for his fundamental contributions to the field of computational molecular biology, specifically for his discoveries in the areas of G protein-coupled receptor (GPCR) signaling and intrinsically disordered proteins. Babu is the Chief Editor of *Molecular Systems Biology* and an executive editor of *Nucleic Acids Research*. He is an elected member of EMBO (2016), Fellow of the Royal Society of Chemistry (2017) and Fellow of the UK Academy of Medical Science (2021).

1:45 - 2:15 PM

Craig W. Lindsley

William K. Warren, Jr. Chair in Medicine
University Professor of Pharmacology, Chemistry and Biochemistry
Director, Warren Center for Neuroscience Drug Discovery
Vanderbilt University

Discovery and Development of GPCR Allosteric Ligands: From Concept to Clinic

This talk will focus on Vanderbilt's Warren Center for Neuroscience Drug Discovery, an academic drug discovery center, focused on neuroscience drug discovery and, in particular, allosteric modulation of GPCRs. It will include M1, M4 and M5 programs, and how we de-risked an M1 PAM and entered Phase I without an industrial partner. Then, our Parkinson's disease portfolio, and in particular, our mGlu4 PAM program, which is also in Phase I trials via a start-up company we spun out of the Center will be discussed. Overall, this talk will feature deep basic and translational science applied to successful drug discovery programs.

About the Speaker

Craig W. Lindsley, PhD, is the Director of the Warren Center for Neuroscience Drug Discovery (WCNDD), University Professor and Editor-in-Chief of the *Journal of Medicinal Chemistry*. Lindsley graduated in 1992 from California State University, Chico with a BS in chemistry, and received his PhD degree in chemistry from the University of California, Santa Barbara (Lipshutz), in 1996, and pursued postdoctoral studies at Harvard University (Shair). In 2001, Craig accepted a position at Merck & Co. In 2006, Craig accepted an Associate Professor position in Pharmacology and Chemistry at Vanderbilt University, and was promoted to full professor in 2009. In that same year, Craig became the founding Editor-in-Chief of *ACS Chemical Neuroscience* and was also awarded the ASPET-Astellas Award for Translational Pharmacology. In 2012, he was awarded the William K. Warren, Jr. Endowed Chair in Medicine. The following year, Lindsley was awarded the Portoghese Lectureship from the ACS MEDI division and the *Journal of Medicinal Chemistry* for impact in the field of medicinal chemistry, and in 2014, received the John J. Abel Award in Pharmacology from ASPET. More recently, Lindsley was inducted as an AAAS Fellow, awarded the Pharmacia-ASPET Award in Experimental Therapeutics and named a Thomson Reuters Highly Cited Researcher (2015, 2016 and 2017) as well as one of Thomson Reuters World's Most Influential Scientific Minds (2016). In 2018, he was honored as the 22nd Smissman Memorial Lecturer (KU Department of Medicinal Chemistry) and the 2018 Sato Memorial International Award. Together with Jeff Conn, Lindsley has pioneered the concept of GPCR allosteric modulation, developing key proof of concept compounds and clinical candidates. He holds over 104 issued US patents and has published over 530 manuscripts and another 200 published patent applications. As co-founder and Director of the WCNDD, Lindsley has raised over $290 million in licensing and research support from NIH, Foundations and companies.

2:15 - 2:45 PM

Marvin J. Miller

Professor Emeritus
University of Notre Dame

Design, Syntheses and Studies of New Antibiotics

New or repurposed antibiotics are desperately needed since bacterial resistance has risen to essentially all of our current antibiotics and few new antibiotics have been developed over the last several decades. A primary cause of drug resistance is the overuse of antibiotics that can result in alteration of microbial permeability, alteration of drug target binding sites, induction of enzymes that destroy antibiotics (i.e., beta-lactamases) and even induction of efflux mechanisms. A combination of chemical syntheses, microbiological and biochemical studies demonstrate that the known critical dependence of iron assimilation by microbes for growth and virulence can be exploited for the development of new approaches to antibiotic therapy. Iron recognition and active transport relies on the biosyntheses and use of microbe-selective iron chelating compounds called siderophores. Our studies, and those of others, demonstrate that siderophores and analogs can be used for iron transport-mediated drug delivery ("Trojan Horse" antibiotics or sideromycins) and induction of iron limitation/starvation (development of new agents to block iron assimilation). Several examples will illustrate that, aided by chemical syntheses, this approach can generate microbe selective antibiotics. The scope and limitations of this approach, especially related to "microbe adaptability" and development of resistance, siderophore-based molecular recognition requirements, appropriate linker and drug choices will be described.

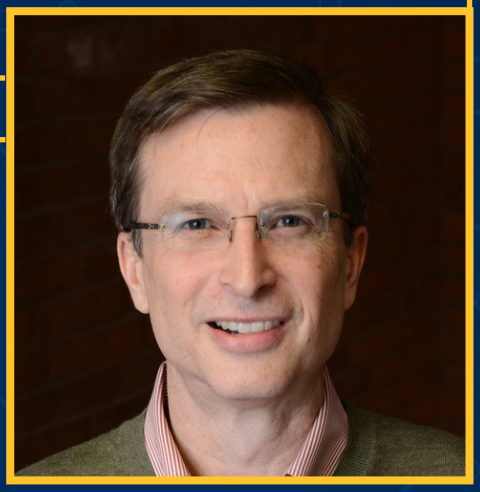
About the Speaker

For nearly 40 years, Marvin Miller has made countless contributions to medicinal chemistry, focusing on a mixture of synthetic organic chemistry and bioorganic chemistry to develop new methods in an effort to study, prevent, and cure disease, in particular tuberculosis and bacterial infections. Miller received his BS in chemistry from North Dakota State University in 1971 and his PhD in bioorganic chemistry from Cornell University in 1976 under the direction of G. Marc Loudon. He was a National Institutes of Health fellow postdoctoral fellow in the laboratory of Professor Henry Rapoport at the University of California at Berkeley (1975-77). He then joined the Notre Dame College of Science faculty and served as an Assistant Professor from 1977 onward. In 1996, Miller was named the George & Winifred Clark Professor of Chemistry and Biochemistry at the University of Notre Dame. Miller has over 300 peer reviewed publications and more than 25 US patents. As a popular lecturer across the country and around the world, he has mentored more than 80 graduate students and 70 postdoctoral researchers and visiting scientists.

3:00 - 3:30 PM

Craig M. Crews

John C. Malone Professor of Molecular, Cellular, and Developmental Biology
Department of Chemistry & Department of Pharmacology
Yale University



PROTAC-mediated Protein Degradation: A New Therapeutic Modality

The Crews lab is interested in using 'Applied Chemical Biology' to develop novel therapeutic modalities. Enzyme inhibition has proven to be a successful paradigm for pharmaceutical development; however, it has several limitations. As an alternative, for the past 20 years, we focused on developing Proteolysis Targeting Chimera (PROTAC), a new 'controlled proteolysis' technology that overcomes the limitations of the current inhibitor pharmacological paradigm. Based on an 'Event-driven' paradigm, PROTACs offer a novel, catalytic mechanism to irreversibly inhibit protein function, namely, the intracellular destruction of target proteins. This approach employs heterobifunctional molecules capable of recruiting target proteins to the cellular quality control machinery, thus leading to their degradation. We have demonstrated the ability to degrade a wide variety of targets (kinases, transcription factors, epigenetic readers) with PROTACs at picomolar concentrations. Moreover, the PROTAC technology has been demonstrated with multiple E3 ubiquitin ligases and now two PROTAC-based drug candidates are being tested in clinical trials for prostate and breast cancer.

About the Speaker

Craig Crews, PhD, is the John C. Malone Professor of Molecular, Cellular, and Developmental Biology Department and professor of Chemistry and Pharmacology at Yale University. He graduated from the University of Virginia with a BA in chemistry and received his PhD from Harvard University in biochemistry. On the faculty at Yale since 1995, his laboratory has developed the use of small molecules to control intracellular protein levels. In 2003, he co-founded Proteolix, Inc., whose proteasome inhibitor, Kyprolis™ received FDA approval for the treatment of multiple myeloma. Crews' lab is also credited with founding the field of 'Targeted Protein Degradation' drug development technology, i.e., PROTACs, which has the potential to target currently 'undruggable' disease causing proteins. In 2013, Crews launched the New Haven-based biotech venture, Arvinas, Inc., which is testing the first PROTAC-based drugs in clinical trials for prostate and breast cancer. Crews has received numerous awards and honors, including the Ehrlich Award for Medicinal Chemistry (2014), a NIH R35 Outstanding Investigator Award (2015), the AACR Award for Outstanding Achievement in Chemistry in Cancer Research (2017), the Khorana Prize from the Royal Society of Chemistry (2018), the Pierre Fabre Award for Therapeutic Innovation (2018), the Pharmacia-ASPET Award for Experimental Therapeutics (2019), the Heinrich Wieland Prize (2020) and the Scheele Prize (2021).

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