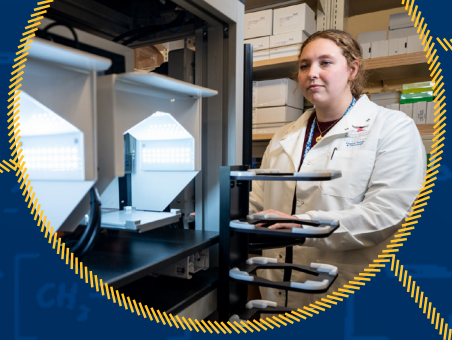
$B \Rightarrow c^2 m$

Bringing Chemistry to Medicine

2022 Symposium

St. Jude Children's Research Hospital®

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



Bringing Chemistry to Medicine

Virtual Symposium

$$B \Rightarrow c^2 m$$

The Bringing Chemistry to Medicine Symposium features thought leaders at the interface of chemical and biomedical sciences.

Transcription Therapy: *Thursday, July 21*

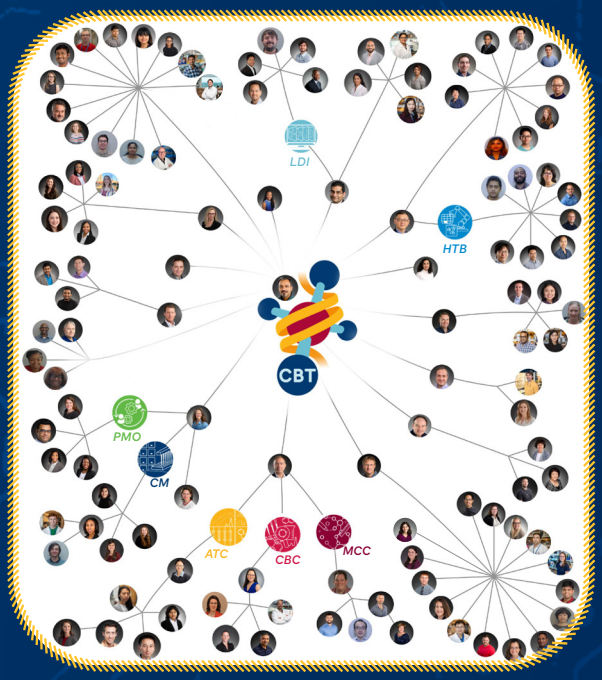
and

Frontiers in Chemical Biology: *Friday, July 22*

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.

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

St. Jude Cancer Center

The St. Jude Comprehensive Cancer Center, led by director Charles W. M. Roberts 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.

July 21: Transcription Therapy

9:00-9:15 AM CDT	**Opening Remarks** **Charles W.M. Roberts & Aseem Z. Ansari**	
9:15-9:55	**Fraydoon Rastinejad**	**Visualizing Drug-Binding Pockets in Transcription Factors**
9:55-10:35	**Bradley Bernstein**	**Etiology and Impact of Methylation Changes in Cancer**
10:35-10:45	**Break**	
10:45-11:25	**Kenneth S. Zaret**	**Overcoming Chromatin Barriers for Transcription Therapies**
11:25-12:05	**Geeta J. Narlikar**	**Mechanism of the INO80 ATP-dependent chromatin remodeling machine**
12:05-1:15	**Lunch**	
1:15-1:55	**Clifford P. Brangwynne**	**Intracellular Phase Transitions: The Fluidity of Biological Function**
1:55-2:35	**Tanja Mittag**	**Transcriptional Hubs or Condensates?**
2:35-2:45	**Break**	
2:45-3:25	**Jolanta Grembecka**	**Therapeutic Targeting of Epigenetic Modifiers in Leukemia**
3:25-4:05	**Scott A. Armstrong**	**Therapeutic Targeting of Chromatin Complexes in Cancer**
4:05-4:35	**Discussion**	
4:35-4:45	**Closing Remarks** **Aseem Z. Ansari**	

July 22: Frontiers in Chemical Biology

9:00-9:10 AM CDT	**Opening Remarks** **Aseem Z. Ansari**	
9:10-9:50	**Peter G. Schultz** Intro: Hai Dao	**A Chemist's Foray into Translational Research**
9:55-10:25	**Derek S. Tan** Intro: Scott Blanchard	**SEAKERs: Targeted Cellular Micropharmacies that Generate Small-Molecule Drug in situ**
10:25-10:40	**Break**	
10:45-11:15	**Ron Dror** Intro: Marcus Fischer	**Molecular Simulation and Machine Learning for the Design of Finely Tuned Drugs**
11:20-11:50	**Judith P. Klinman** Intro: Marcus Fischer	**Integrating Protein Dynamics into Enzyme Function**
12:00-1:00	**Lunch**	
1:05-1:35	**Matt D. Disney** Intro: Richard Lee	**Sequence-based Design of Small Molecules Targeting RNA Structures to Manipulate and Study**
1:35-2:10	**David D. Moore** Intro: Taosheng Chen	**Regulation of Liver Energy Balance by Nutrient-sensing Nuclear Receptors**
2:10-2:45	**Dorothee Kern** Intro: Tommaso Cupido	**Protein Dynamics at the Heart of New Cancer Drug Design Approaches**
2:45-3:00	**Break**	
3:00-3:35	**Raymond J. Deshaies** Intro: Zoran Rankovic	**The Awesome Power of Synthetic Organic Chemistry in Drug Development**
3:35-4:10	**Daniel Blair** Intro: Anang Shelat	**Modularized Molecule Making**
4:10-4:40	**Discussion**	
4:40-4:45	**Closing Remarks** **Aseem Z. Ansari**	

St. Jude Children's Research Hospital
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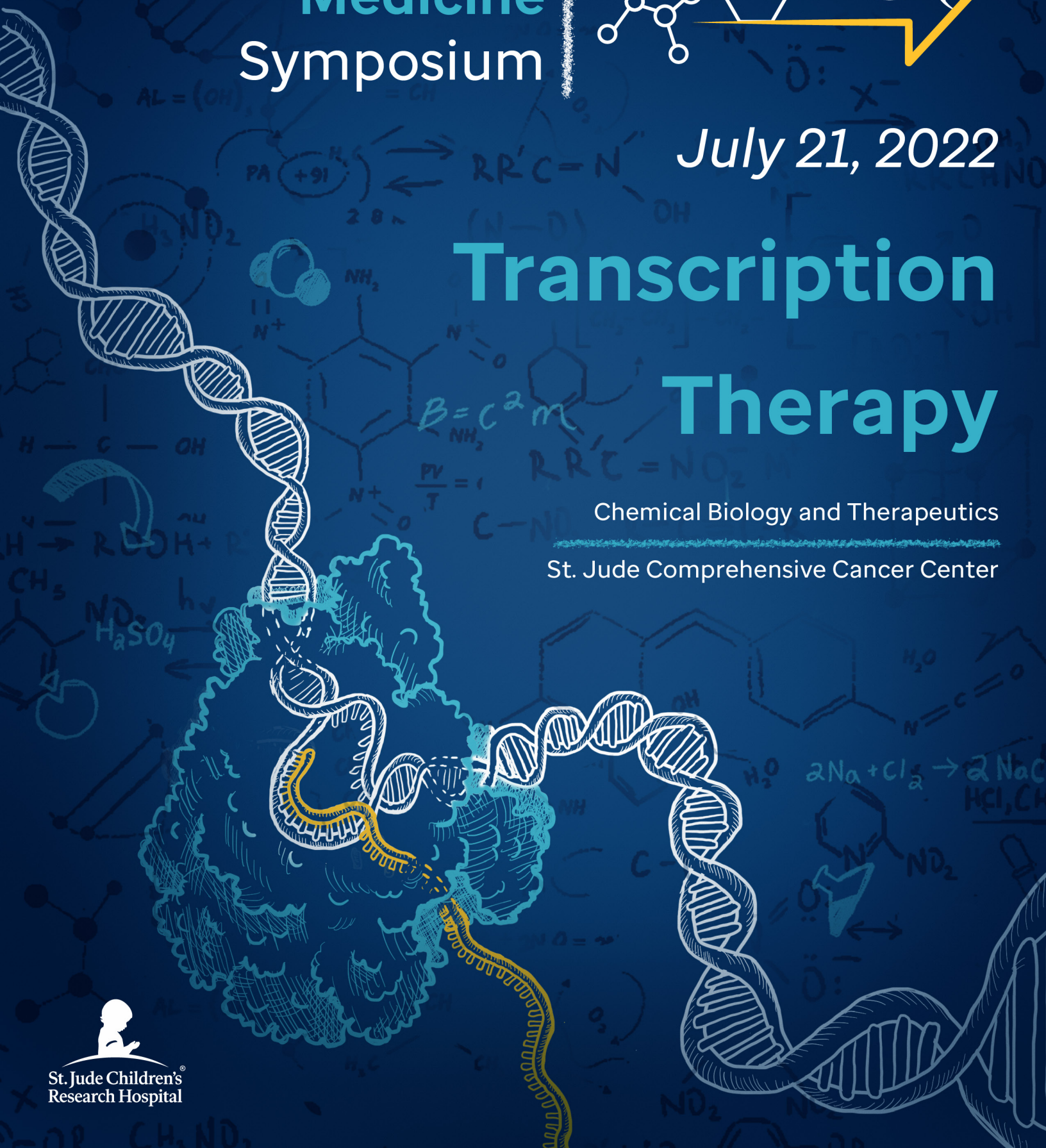
Bringing Chemistry to Medicine Symposium

July 21, 2022

Transcription Therapy

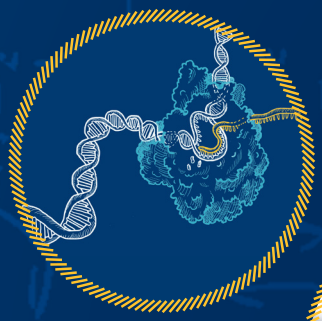
Chemical Biology and Therapeutics

St. Jude Comprehensive Cancer Center



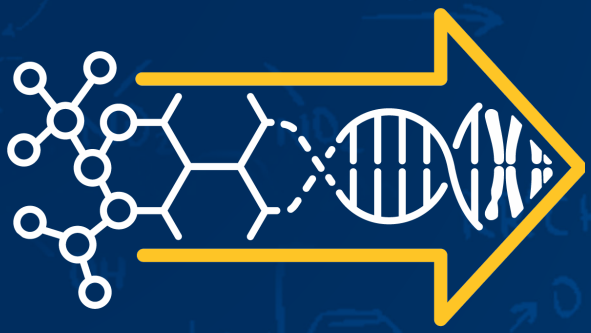
St. Jude Children's Research Hospital®

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 c²m Symposium



Our research and commitment is not limited to St. Jude. We collaborate with leading scientific and clinical institutions around the world to understand and develop cures for childhood diseases. A key objective for juxtaposing scientists studying gene regulation (Transcription Therapy -day 1) with chemical biologists (Frontiers in Chemical Biology -day 2) is to bring together leaders from both communities to envision new solutions for disease-causing malfunctions in gene transcription. Building on the success of this symposium series, we are working to engage the global scientific community to develop innovative Transcription-targeted Therapies for a wide-range of human diseases. We invite you to join us in this endeavor.

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

Charles W. M. Roberts

Executive Vice President

Director, Comprehensive Cancer Center

Aseem Z. Ansari

Chair, Chemical Biology & Therapeutics

R. J. Ulrich Endowed Chair

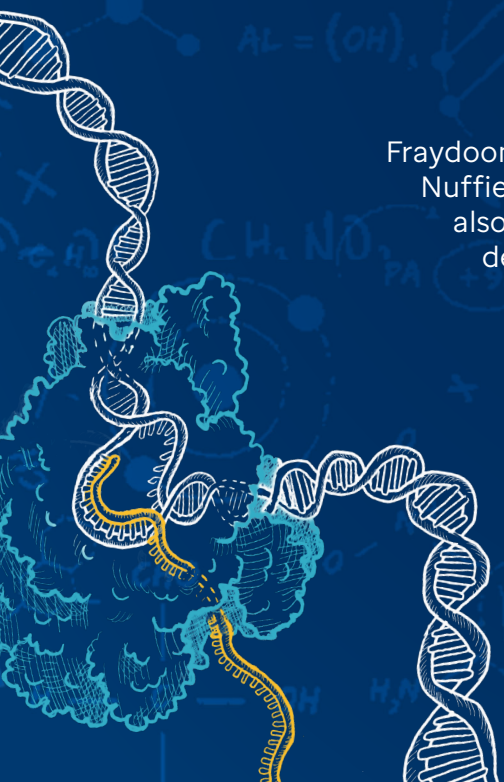
9:15 - 9:55 AM

Fraydoon Rastinejad

Professor of Biochemistry
Wellcome-Trust Senior Investigator
Nuffield Department of Medicine, University of Oxford

Visualizing Drug-Binding Pockets in Transcription Factors

The unifying theme of our research is to develop stereochemical and mechanistic understanding of ligand-dependent transcription factors and their functions as gene regulators. Recently, our emphasis has focused on the bHLH-PAS family of human transcription factors. These include the hypoxia-inducible factors (HIF-1α HIF-F2α HIF-3α), Aryl hydrocarbon receptor (AhR), neuronal PAS domain proteins (NPAS1, NPAS2, NPAS3, NPAS4), single minded proteins (SIM1, SIM2) and their common heterodimeric partners ARNT or ARNT2. We began by visualizing multi-domain HIF-1α/ARNT and HIF-2α/ARNT architectures to identify their multi-domain architectures and their druggable pockets. These studies focused on functional complexes that included their bound DNA elements and small-molecule ligands. The structures revealed how all these components are simultaneously accommodated within these HIF complexes to allow for bidirectional control of their functions as transcription factors. We then expanded to include NPAS1/ARNT and NPAS3/ARNT heterodimeric complexes and found an overall conservation of their architectures but with unique drug-binding cavities inside their PAS domains. Examining the architecture of the Bmal1/Clock heterodimer, we find it too harbors distinct ligand-binding pockets where-molecules could impact the functional outputs of core clock components. These findings together are now projecting the entire human bHLH-PAS proteins to constitute a previously unrecognized class of ligand-dependent transcription factors, comparable to the nuclear receptor family. Given their key roles in several unmet disease arenas, we are subjecting this family to in-depth chemical and functional interrogations including high-throughput screens to identify the first small-molecule modulators for each protein.



About the Speaker

Fraydoon Rastinejad is Professor of Biochemistry at the University of Oxford, Nuffield Department of Medicine, and a Wellcome-Trust Senior Investigator. He is also a Senior Kurti Fellow at Brasenose College, Oxford. He received bachelor's degrees from Northwestern University in Mathematics and in Biochemistry, and a Ph.D. degree in Biophysics from University of Pennsylvania. He was a postdoctoral fellow with Paul Sigler at Yale University, where his interests in structural characterization of gene-regulatory complexes first began. His laboratory at Oxford focuses on exploring the atomic structures and small-molecule binding capabilities of transcription factors that regulate gene programs in response to nutritional, hormonal, and environmental signals. Dr. Rastinejad is Fellow of Royal Society in Biology and is also co-founder of Flare Therapeutics in Cambridge, MA.

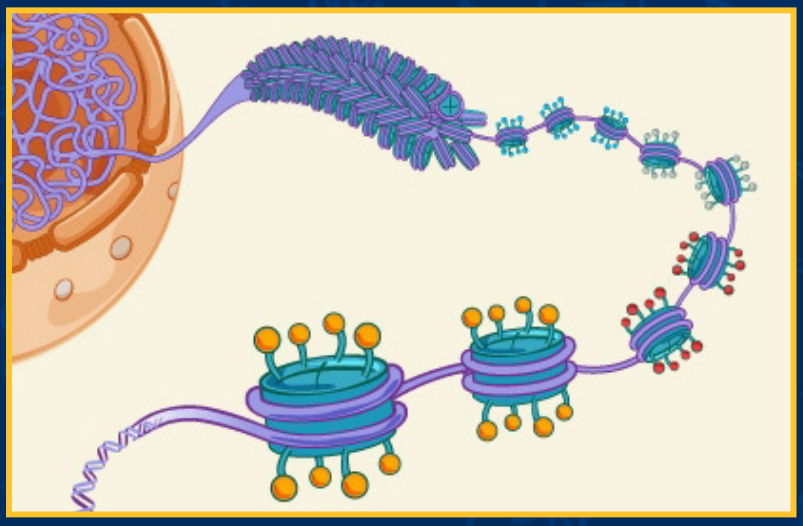
9:55 - 10:35 AM

Bradley Bernstein

Chair of Cancer Biology
Dana Farber Cancer Institute

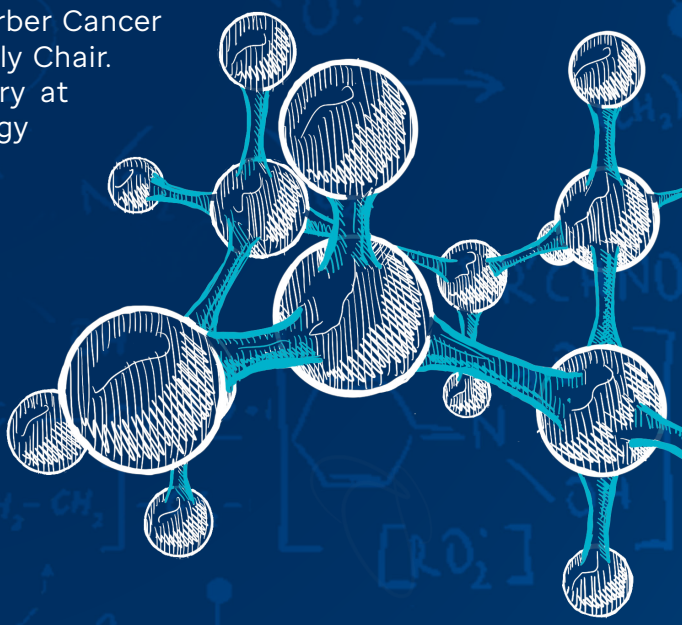
Etiology and Impact of Methylation Changes in Cancer

Bernstein will discuss recent studies of the global and locus-specific methylation changes and their impact on tumor biology.



About the Speaker

Bradley Bernstein is Chair of Cancer Biology at the Dana-Farber Cancer Institute, where he holds the Richard and Nancy Lubin Family Chair. He is also the Director of the Gene Regulation Observatory at the Broad Institute, a Professor of Cell Biology and Pathology at Harvard Medical School, and an Investigator in Harvard's Ludwig Institute. He served on the faculty at Massachusetts General Hospital from 2005 to 2021. Bernstein's research focuses on epigenetic gene regulation in stem cells and cancer. His work has been recognized by an Early Career Scientist Award from the Howard Hughes Medical Institute, a Career Award in the Biomedical Sciences from the Burroughs Wellcome Fund, the NIH Director's Pioneer Award, an American Cancer Society Professorship, and the Paul Marks Prize for Cancer Research.



10:45 - 11:25 AM

Kenneth S. Zaret

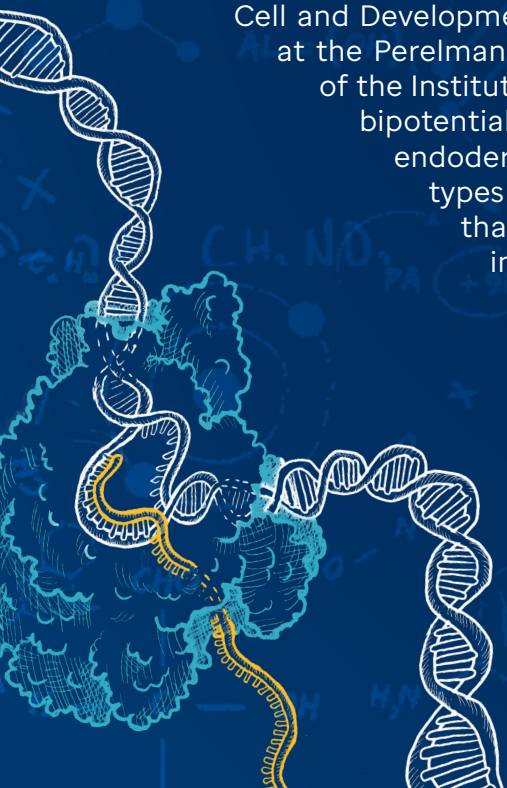
Joseph Leidy Professor, Department of Cell and Developmental Biology
Director, Institute for Regenerative Medicine
University of Pennsylvania Perelman School of Medicine

Overcoming Chromatin Barriers for Transcription Therapies

The discovery of transcription factors that normally induce embryonic tissues, adult regeneration, and disease has inspired the ectopic expression of such factors to re-wire genetic networks. Yet the ectopic expression of transcription factors does not change cell fate sufficient for long-term therapies or tissue reconstitution in transplantation contexts, demonstrating insufficient restructuring of genetic networks. Our lab takes two approaches to this problem: First, we investigate how pioneer transcription factors engage silent chromatin and perturb an underlying nucleosome, to enable nucleosome remodelers and other components to activate target genes. Second, we found that H3K9me3-heterochromatin is a barrier to gene activation during development and during cellular reprogramming. We performed a functional protein screen to understand how different H3K9me3-heterochromatin proteins target different classes of genes. Our work indicates that coupling ectopic transcription factors with a transient heterochromatin protein knockdown, as a therapy, could a stronger change in genetic network response.

About the Speaker

Kenneth Zaret obtained his Ph.D. in Biophysics from the University of Rochester School of Medicine in 1982 and was a Postdoctoral Fellow at UC San Francisco until 1985. In 1986-1999, he rose to Professor of Biomedical Sciences at Brown University, RI, and in 1999-2009 he held the W.W. Smith Chair in Cancer Research at the Fox Chase Cancer Center, where he also served as Program Leader of Cell and Developmental Biology. Since 2009, Dr. Zaret has been the Joseph Leidy Professor at the Perelman School of Medicine at UPenn, and since 2014, he has been the Director of the Institute for Regenerative Medicine at UPenn. Dr. Zaret's laboratory discovered a bipotential precursor population for liver and pancreas progenitors in the embryonic endoderm. They showed that inductive signals from two distinct mesodermal cell types coordinately control the liver vs. pancreas fate decision. They also discovered that the liver emanates from two distinct domains in the foregut endoderm, induced by signaling in different ways. They discovered that endothelial cells signal to the liver and pancreas progenitors to promote morphogenesis, independent of blood flow; as subsequently seen in diverse contexts. Dr. Zaret's group discovered and named "pioneer transcription factors" that bind to silent chromatin, endowing the competence for cell differentiation and promoting cellular reprogramming. They found that silent chromatin binding is imparted by the inherent ability of pioneer factors to recognize their target motif, or a partial motif, on the surface of a nucleosome. His laboratory's findings on the mechanisms of gene, cell, and tissue induction have provided numerous insights for reprogramming cell fate for applications in disease models and future therapies.



11:25 - 12:05 AM

Geeta J. Narlikar

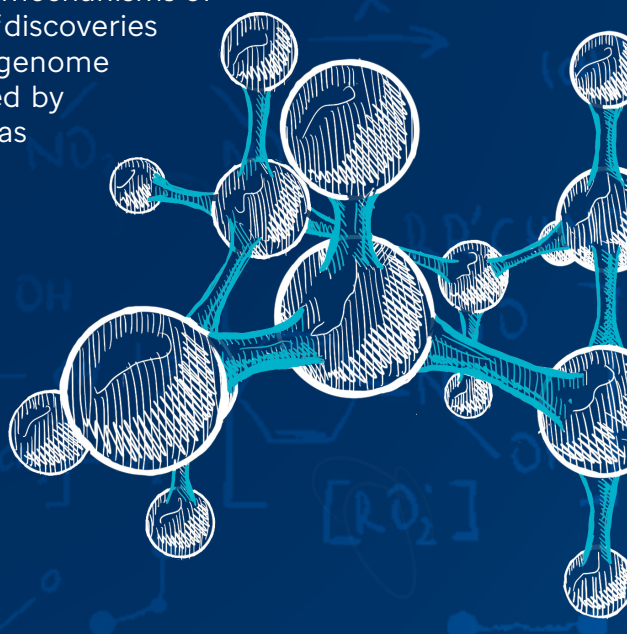
Professor, Biochemistry and Biophysics
Lewis and Ruth Cozen Chair I
University of California, San Francisco

Mechanism of the INO80 ATP-dependent chromatin remodeling machine

The critical role of the INO80 chromatin-remodeling complex in transcription is commonly attributed to its nucleosome sliding activity. We found that INO80 prefers to mobilize hexasomes over nucleosomes by ~60-fold. INO80's preference for hexasomes is highest when linker DNA lengths approach the ~18 bp linkers in yeast gene bodies. Correspondingly, deletion of INO80 significantly affects the positions of hexasome-sized particles within yeast genes in vivo. Our results suggest that the Arp5 and Ies6 subunits of INO80 promote nucleosome sliding by dislodging an H2A/H2B dimer, thereby making a nucleosome transiently resemble a hexasome. We propose that this mechanism allows INO80 to rapidly mobilize nucleosomes at promoters and hexasomes within gene bodies. Rapid repositioning of hexasomes that are generated in the wake of transcription may mitigate spurious transcription. More generally, such versatility may explain how INO80 regulates chromatin architecture during the diverse processes of transcription, replication and repair.

About the Speaker

Dr. Narlikar obtained her Ph.D. in Chemistry at Stanford University under the mentorship of Dr. Daniel Herschlag and carried out postdoctoral research at Harvard Medical School under the mentorship of Dr. Robert Kingston. She has been a faculty member in the Department of Biochemistry and Biophysics at UCSF since 2003. She is an expert in the fields of epigenetic regulation and genome organization. Dr. Narlikar studies how the folding and compartmentalization of our genome is regulated to generate the many cell types that make up our body. Her laboratory has pioneered the application of sophisticated biophysical approaches to study the mechanisms of macromolecules that regulate genome organization. These types of discoveries from the Narlikar laboratory are changing textbook descriptions of genome packaging and suggesting new avenues to tackle diseases caused by defects in genome organization. Dr. Narlikar's scientific work has been recognized by different awards during the course of her faculty career. These include the Beckman Young Investigator Award (2006), the Leukemia and Lymphoma Society Scholar Award (2008), the Outstanding Faculty Mentorship Award by the UCSF Graduate Students Association (2011), the Deleage Prize awarded by the Deleage foundation (2017), the Glenn Award for Research in Biological Mechanisms of Aging (2018), and the Distinguished Alumnus Award from the Indian Institute of Technology, Mumbai (2018). Since 2017, Professor Narlikar has been appointed to the Lewis and Ruth Cozen Chair I. She was elected to the National Academy of Sciences in 2021.



1:15 - 1:55 PM

Clifford P. Brangwynne

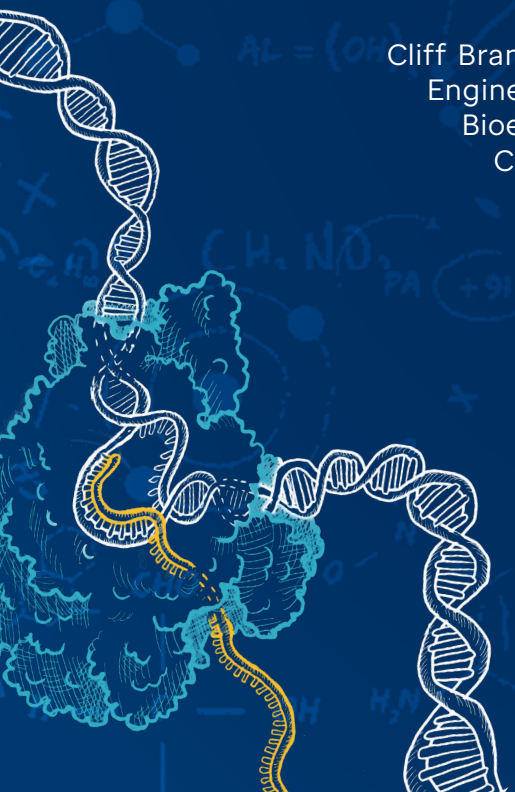
Director, Princeton Bioengineering Initiative
Professor, Chemical and Biological Engineering
Princeton University

Intracellular Phase Transitions: The Fluidity of Biological Function

In this talk I will discuss our work to understand and control intracellular phase transitions, which we've discovered play an important role in organizing the contents of living cells. Membrane-less RNA and protein rich condensates are found throughout the cell, and are associated with myriad biological functions. Liquid-liquid phase separation (LLPS) and related phase transitions underlie the assembly of many of these structures. LLPS plays a role in various condensate features, for example the structural organization of the nucleolus, which has important consequences for sequential ribosomal RNA processing. Our lab has also developed a suite of technologies that allowing us to probe and engineer condensates in both the cytoplasm and nucleus. We are using these tools to quantitatively map intracellular phase behavior, providing unprecedented access to the biophysical principles underlying condensate assembly and function. These approaches have begun to yield rich insights into the link between condensate viscoelasticity, and cell physiology and disease, and are suggesting new strategies for therapeutic intervention in diseases ranging from cancer and neurodegeneration to viral infections.

About the Speaker

Cliff Brangwynne is the June K. Wu '92 Professor of Chemical and Biological Engineering at Princeton University, and Director of the Princeton Bioengineering Initiative. He obtained a B.S. in Materials Science from Carnegie Mellon University in 2001, and PhD in Applied Physics in 2007 from Harvard University. He was a visiting fellow at the Max Planck Institute for the Physics of Complex Systems in Dresden, and was a Helen Hay Whitney Postdoctoral Fellow at the Max Planck Institute for Molecular Cell Biology and Genetics in Dresden. Since 2011 he has been a faculty member in the Department of Chemical and Biological Engineering at Princeton University. His primary research interests are in biological self-assembly, particularly in the role of intracellular liquid-liquid phase separation. Dr. Brangwynne is the recipient of numerous awards including a Searle Scholar Award, a Macarthur Fellowship, Wiley Prize, HFSP Nakasone Award, and he is a Howard Hughes Medical Institute Investigator.

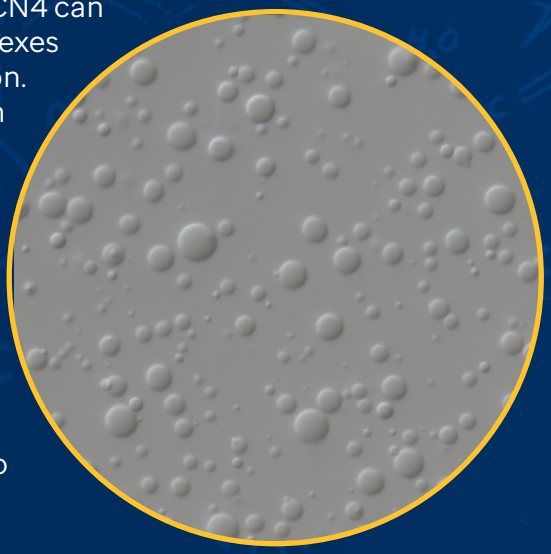


Tanja Mittag

Member, Department of Structural Biology
St. Jude Children's Research Hospital

Transcriptional Hubs or Condensates?

Transcription is a temporally and spatially highly regulated process in which the transcription apparatus must efficiently assemble at specific genomic sites. Recent studies suggest that phase separation is responsible for the spatial organization of transcription at super-enhancers. Aberrant transcriptional programs mediated by certain fusion-oncoproteins also seem to rely on phase separation. However, whether phase separation is required for transcription in general or whether transcription is instead mediated by discrete complexes (or so-called hubs) of transcription factors and downstream machinery such as the mediator is still an open question. Here we test if the activity of the canonical yeast transcription factor GCN4 can be explained via phase separation or instead by discrete complexes with the mediator subunit Med15 in the absence of phase separation. We build on our conceptual understanding of phase separation in the context of the sticker-and-spacers framework. Specifically, we consider that the formation of condensates is mediated by phase separation coupled to percolation. While percolation is mediated via multivalent stickers that form physical crosslinks with one another, phase separation is a density transition that requires relatively poor solubility mediated by non-specific interactions, mostly through spacers. We make use of this conceptual framework to attempt to dissociate the function of discrete complexes and condensates. A better understanding of the role of phase separation in transcription has the potential to result in new strategies for therapeutic interventions.



About the Speaker

Tanja Mittag received her PhD from the Johann Wolfgang Goethe University in Frankfurt, Germany, where she used NMR spectroscopy to characterize multistep protein-ligand binding mechanisms. She trained as a Postdoctoral Fellow with Julie Forman-Kay at the Hospital for Sick Children in Toronto, where she revealed how a highly dynamic complex with several interconverting interfaces can encode a cell cycle switch. She joined the Department of Structural Biology at St. Jude Children's Research Hospital in 2010 and became Full Member in 2021. Her lab uses a spectrum of biophysical, biochemical and cell biological tools to elucidate the mechanism underlying phase separation and its roles in physiological and pathological processes. She was awarded the Michael and Kate Bárány Award for Young Investigators from the Biophysical Society (2021) for her rigorous and foundational contributions to the field of macromolecular condensates and their biological relevance.

2:45 - 3:25 PM

Jolanta Grembecka

Associate Professor, Department of Pathology
Co-Leader, Developmental Therapeutics Program
Rogel Cancer Center at the University of Michigan

Therapeutic Targeting of Epigenetic Modifiers in Leukemia

Epigenetic aberrations play a central role in the development of human cancers, including acute leukemia. Modulation of epigenetic marks in cancer cells can be achieved either via direct inhibition of epigenetic modifiers or by affecting their recruitment to chromatin, both of which can lead to the suppression of cancer cell growth. Our efforts have been focused on utilizing both approaches to develop new epigenetic therapies for acute leukemia. First, we will discuss our most recent efforts towards development and advancement of menin-MLL1 inhibitors, one of which has entered clinical trials for AML patients with MLL1-translocations or NPM1-mutations. These efforts resulted in sub-nanomolar menin-MLL1 inhibitors, which as a single agents induce remission of leukemia in the patient-derived xenograft models. Second, we will present examples of direct targeting of epigenetic modifiers by blocking the catalytic activity of histone methyltransferase ASH1L, which has been validated as a target in acute leukemia. Development of the first-in-class small molecule inhibitors of ASH1L together with their activity in relevant leukemia models will be presented.

About the Speaker

Jolanta Grembecka is an Associate Professor in the Department of Pathology and Co-Leader of the Developmental Therapeutics Program in the Rogel Cancer Center at the University of Michigan. Dr. Grembecka's research has been focused on development of small molecule inhibitors of proteins involved in oncogenesis, with a particular focus on leukemia related proteins. Work from Dr. Grembecka's laboratory has been dedicated to developing small molecules targeting the protein-protein interaction between menin and Mixed Lineage Leukemia 1 (MLL1) as a new targeted therapy for acute leukemia patients with translocations of the MLL1 gene. Her laboratory has developed the first small molecule inhibitors of the menin-MLL1 interaction, which were licensed by Kura Oncology and advanced to phase I/IIA clinical trials in acute myeloid leukemia patients. Her laboratory is also pursuing development of new targeted therapies for hematologic and solid cancers by blocking novel epigenetic targets, including histone methyltransferases. Dr. Grembecka has received her PhD in Chemistry at Wroclaw University of Technology, Poland. She completed postdoctoral training in drug discovery at the University of Virginia, before starting her independent laboratory at the University of Michigan. Dr, Grembecka is a co-author on ~80 peer-reviewed scientific publications and an inventor on over 10 patents. She is a Leukemia and Lymphoma Society Scholar and American Cancer Society Research Scholar.

Scott A. Armstrong

Chair, Department of Pediatric Oncology
Dana Farber Cancer Institute

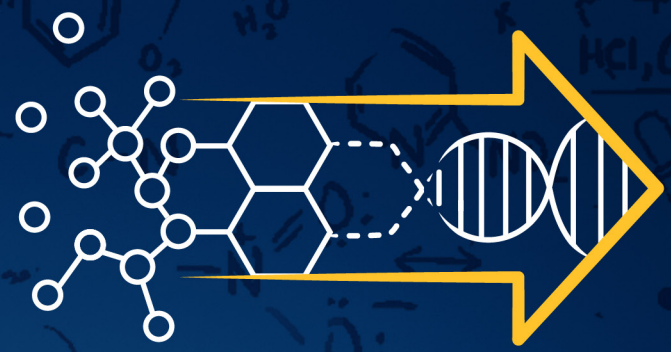
Therapeutic Targeting of Chromatin Complexes in Cancer

Inappropriate expression of genes such as the homeotic (HOX) genes is found in up to 40% of cases of Acute Myelogenous Leukemia (AML). Two well-defined genetic subsets, those with MLL-rearrangements and those with NPM1 mutations, are known to possess high-level expression of HOX and MEIS1 genes and have been shown to be dependent on continued expression of these genes. Recent studies have defined the chromatin-bound protein complexes that maintain this aberrant gene expression. Furthermore, multiple groups including ours have now developed small molecule inhibitors of chromatin-associated complexes. Some of these small molecules, including those targeting DOT1L, EZH2, and Bromodomains are at various stages of clinical development. Another approach to target chromatin associated complexes is via disruption of protein-protein interactions. One such protein-protein interaction that is being targeted is the interaction between the histone methyltransferase MLL1 and Menin, an approach that has also been shown to reverse leukemogenic HOX/MEIS1 gene expression. We have developed novel, potent and orally bioavailable MLL1-Menin inhibitors and have brought one of these small molecules to clinical assessment. Inhibition of the MLL1-Menin interaction in MLL-rearranged and NPM1 mutant AML cells leads to loss of Menin from chromatin, destabilization of the Menin protein and specific changes in chromatin state that include loss of the MLL1 complex at select loci. This results in selective reversal of leukemogenic gene expression, changes in occupancy of multiple other chromatin complexes, rapid cellular differentiation and cell death. Also, we have recently found this interaction to be critical in subtypes of Sarcoma opening up novel potential therapeutic opportunities.

About the Speaker

Scott A. Armstrong is Chair of the Department of Pediatric Oncology at the Dana-Farber Cancer Institute, and the David G. Nathan Professor of Pediatrics at the Dana-Farber Cancer Institute, Boston Children's Hospital, and Harvard Medical School. He is also President of Dana-Farber/Boston Children's Cancer and Blood Disorders Center. Dr. Armstrong's research group has made seminal discoveries into leukemia biology and chromatin based epigenetic mechanisms in cancer. This work has spurred the development of several new classes of therapeutic agents that target epigenetic mechanisms and gene activity in cancer with many already being tested in clinical trials for both children and adults. Dr. Armstrong has served on multiple review committees for the Leukemia and Lymphoma Society and has served multiple roles for the American Association for Cancer Research including as a member of the Board of Directors. His work has been recognized with awards such as the Paul Marks Prize for Cancer Research from Memorial Sloan Kettering Cancer Center, the E. Mead Johnson Award from the Society for Pediatric Research and the Dameshek Prize from the American Society of Hematology. He is a member of the National Academy of Medicine.

Bringing Chemistry to Medicine Symposium



July 22, 2022

Frontiers in Chemical Biology

CBT

Chemical Biology and Therapeutics

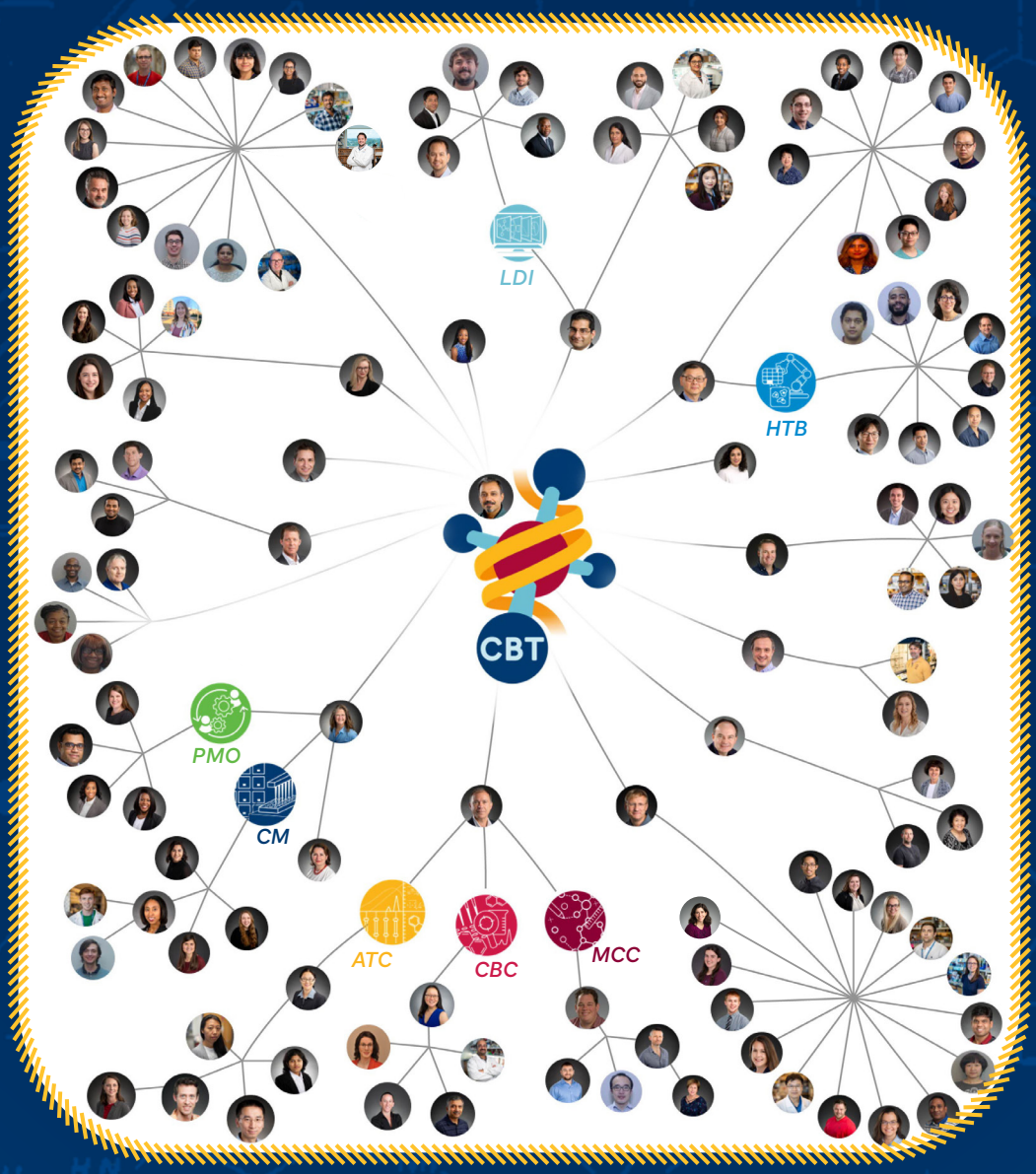
St. Jude Children's Research Hospital®

Chemical Biology and Therapeutics

The mission of St. Jude, to find cures and save children, imbues us with a clarifying sense of purpose. The institution provides agency, a collaborative ecosystem, and resources to tackle major scientific problems.

Chemical Biology and Therapeutics (CBT) is a dynamic department composed of two intertwined halves. One-half of the department, composed of ten academic groups, investigates biology using chemical and computational approaches. The other, composed of seven collaborative centers, is focused on developing novel therapeutic leads for future cures. The centers function as a pharma-scale "Therapeutics" unit, with capabilities that are rarely accessible at academic institutions.

A deep sense of camaraderie binds CBT's diverse community of students, staff and scientists. As a community, we are focused on our defining goal: to bring chemical concepts and tools to explore biology and create new medicines.



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.

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

Chemical Biology Center:
Applies advanced methods to develop sophisticated chemical tools designed to map and interrogate biological and pathological.

Medicinal Chemistry Center:
Identifying and developing potent and selective small molecules

Project Management:
Implements project management practices into the translational drug discovery process

Lead Discovery Informatics:
Chemo-centric informatics infrastructure enabling interrogation of biology through chemistry, computation, and data science

High Throughput Biosciences:
Target identification and validation, assay development, high- throughput and high-content screening, 3D cell culture

Compound Management:
Curates the small molecule library using automation and electronic data management systems

9:15 - 9:50 AM

Peter G. Schultz

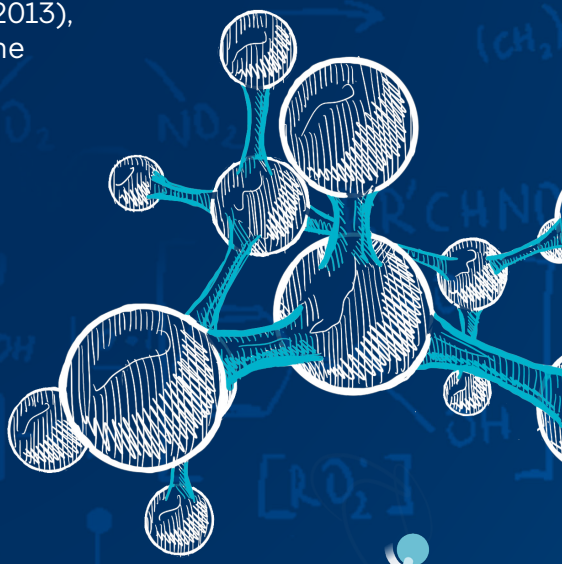
CEO and Professor of Chemistry
The Scripps Research Institute

A Chemist's Foray into Translational Research

We are using a variety of cell-based screens to identify, characterize and optimize small molecules that affect somatic stem cell self-renewal and differentiation in vitro and in vivo as regenerative/reparative therapies. Examples will be discussed including their application to aging and human disease.

About the Speaker

Peter Schultz is the CEO, President, and the Skaggs Presidential Chair Professor at Scripps Research. Schultz is a pioneer in the fields of chemical and synthetic biology. He is also a founder of nine companies that have pioneered the application of molecular diversity technologies to challenges in energy, materials, and human health. Schultz established the Genomics Institute of the Novartis Research Foundation in 1999 and served as its Director until 2010. In 2012, he established Calibr, a nonprofit drug discovery institute. Schultz is the author of more than 600 scientific publications and has trained over 300 coworkers. He has received numerous awards including the Wolf Prize in Chemistry (1994), the Paul Erhlich and Ludwig Darmstaedter Award (2002), the Solvay Prize (2013), the NAS Award in Chemistry and is a member of the National Academy of Sciences, USA (1993) and the Institute of Medicine of the National Academy of Sciences (1998).



Derek S. Tan

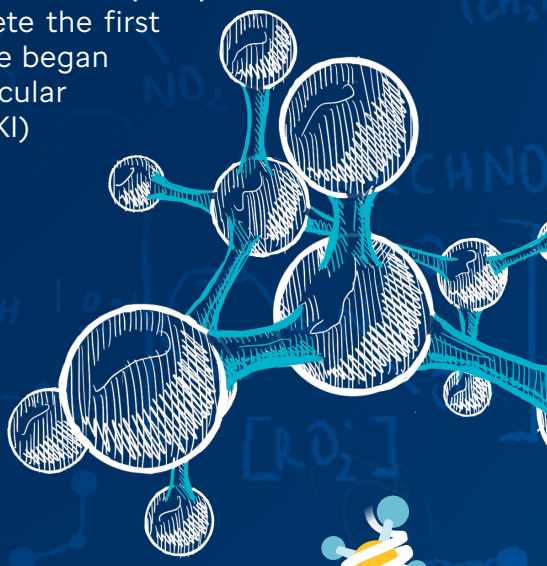
Member and Chair Chemical Biology Program
Memorial Sloan Kettering Cancer Center

SEAKERs: Targeted Cellular Micropharmacies that Generate Small-Molecule Drug in situ

Chimeric antigen receptor (CAR)-T cells represent a major advance in cancer therapy. In this approach, a patient's own T cells are engineered to express a receptor that recognizes a tumor antigen. Upon readministration to the patient, these cells localize to the tumor where they undergo logarithmic proliferation and induce a local cytotoxic immune response to the tumor. However, CAR-T cell therapies face a number of limitations, including escape by antigen-negative cells in heterogeneous tumors, immunosuppression in the tumor microenvironment, eventual exhaustion of T-cell immunologic functions, and limited penetration of solid tumors. To address these challenges, the laboratories of Derek Tan and David Scheinberg at MSK have developed a novel class of CAR-T cells that are engineered to generate synergistic small-molecule drugs locally at tumors. These SEAKER (Synthetic Enzyme-Armed KillER) cells express enzymes that activate systemically administered, non-toxic prodrugs, converting them to the active drugs locally at tumor sites. We demonstrate the effectiveness of this modular platform in vitro and in vivo in mouse tumor models, setting the stage for further advancement of this unique combination therapy strategy.

About the Speaker

Derek S. Tan was born and raised in Rochester, New York. His parents, both chemists at Eastman Kodak, discouraged him from going into chemistry, and so, naturally, he became a chemist. He received his BS in Chemistry from Stanford University in 1995, working with Prof. Dale G. Drueckhammer on the dynamic enzymatic resolution of thioesters. He then went onto graduate studies with Prof. Stuart L. Schreiber at Harvard University, carrying out early research in the field of diversity-oriented synthesis. His work included the synthesis of a combinatorial library of over two million polycyclic small molecules derived from shikimic acid. After receiving his PhD in Chemistry in 2000, he joined the laboratory of Prof. Samuel J. Danishefsky at the Memorial Sloan Kettering Cancer Center (MSK), where he studied natural products total synthesis and helped complete the first total synthesis of the novel terpenoid antibiotic, guanacastepene A. He began his independent career in 2002 as an Assistant Member in the Molecular Pharmacology & Chemistry Program in the Sloan Kettering Institute (SKI) at MSK, and was appointed as a Tri-Institutional Assistant Professor at The Rockefeller University and Weill Cornell Medical College in 2003. He was promoted to Associate Member and Tri-Institutional Associate Professor in 2008 and to tenured Member in 2012 and Tri-Institutional Professor in 2013. In 2015, he was appointed Chair of the newly formed Chemical Biology Program in SKI, where he has recruited three new junior faculty members to date. He was named the incumbent of the Eugene W. Kettering Chair in 2020. Since 2012, he has also served as Director of the Tri-Institutional PhD Program in Chemical Biology, a leading graduate program offered jointly by MSK, The Rockefeller University, and Weill Cornell Medical College.



10:45 - 11:15 AM

Ron Dror

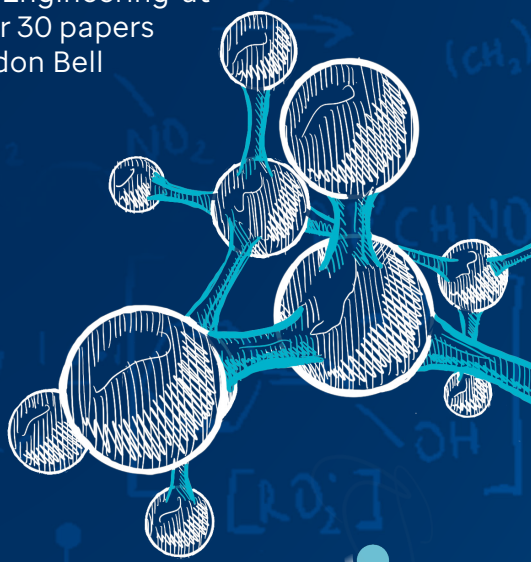
Associate Professor, Computer Science
Stanford University

Molecular Simulation and Machine Learning for the Design of Finely Tuned Drugs

Recent years have seen dramatic advances in experimental determination and computational prediction of macromolecular structure. These structures hold great promise for the discovery of highly effective drugs with minimal side effects, but structure-based design of such drugs remains challenging. I will describe recent progress toward this goal, using both atomic-level molecular simulations and machine learning on three-dimensional structures.

About the Speaker

Ron Dror is an Associate Professor of Computer Science in the Stanford Artificial Intelligence Lab. He is also affiliated with the Departments of Structural Biology and of Molecular and Cellular Physiology, the Institute for Computational and Mathematical Engineering, Bio-X, and ChEM-H. Dr. Dror leads a research group that uses molecular simulation and machine learning to elucidate biomolecular structure, dynamics, and function, and to guide the development of more effective medicines. He collaborates extensively with experimentalists in both academia and industry. Before moving to Stanford, Dr. Dror served as second-in-command of D. E. Shaw Research, a hundred-person company, having joined as its first hire. Dr. Dror earned a PhD in Electrical Engineering and Computer Science at MIT, where he developed machine learning methods for computer vision and genomics. He earned an MPhil in Biological Sciences as a Churchill Scholar at the University of Cambridge, as well as undergraduate degrees in Mathematics and in Electrical and Computer Engineering at Rice University, summa cum laude. He has published over 30 papers in Nature, Science, and Cell, and has won several Gordon Bell Prizes and Best Paper Awards.



Judith P. Klinman

Professor of the Graduate School
Departments of Chemistry and of Molecular and Cell Biology
University of California, Berkeley

Integrating Protein Dynamics into Enzyme Function

While it is well recognized that globular problems are dynamic entities, undergoing a wide range of motions, the ongoing challenge is to link these motions to both theenormous rate accelerationsprovided by enzymesand their accompanying high chemical, regio and stereospecificity. From formal treatmentsof nuclear tunneling in enzymatic C-H activation aprimary role for thermal activation of the surrounding protein scaffoldbecomes apparent. Methodology for the identification of site specific thermal networks and their dynamicalbehavior in enzymes will be discussed. These findings have ramifications for the formulation of the originsof enzyme catalysis. (Supported by funding fromthe NIGMS).

About the Speaker

Dr. Klinman received her A.B. and Ph.D. from the University of Pennsylvania in l962 and l966 and then carried out postdoctoral research with Dr. David Samuel at the Weizmann Institute of Science, Israel, and Dr. Irwin Rose at the Institute for Cancer Research, Philadelphia. She was an independent researcher at the Institute for Cancer Research for several years, before moving to the University of California at Berkeley in l978, where she is now a Distinguished Professor of the Graduate School in the Department of Chemistry, the Department of Molecular and Cell Biology, and the California Institute for Quantitative Biosciences (QB3). She received the National Medal of Science in 2014 and is a member of the American Academy of Arts and Sciences, the National Academy of Sciences, and the American Philosophical Society. Dr. Klinman has been focused on understanding the fundamental properties that underlie enzyme catalysis. In the early stages of her career, she developed the application of kinetic isotope effects to the study of the chemical mechanisms catalyzed by enzymes. In l990, she demonstrated the presence of the neurotoxin, 6-hydroxydopa quinone (referred to as TPQ), at the active site of a copper-containing amine oxidase from bovine plasma, overcoming years of incorrect speculation regarding the nature of the active site structure and opening up the field of protein-derived quino-cofactors. More recent work has unraveled the enigmatic pathway for production of the free-standing bacterial cofactor/vitamin, pyrroloquinoline quinone. Many of the redox enzymes studied in the Klinman laboratory use molecular oxygen as substrate. She developed a set of experimental probes for determining both mechanism and reactive intermediates in oxygen activation and, in the process, has unraveled the mechanism of numerous copper-and iron-dependent enzyme systems. Her most recent investigations are directed at expanding the principles learned from hydrogen transfer processes to other classes of enzyme reaction that include the broad chemical reactivity achieved within the TIM barrel superfamily. These studies have uncovered a role for discrete protein networks that enable site specific thermal transmission from protein-solvent interfaces to the regions of catalysis.

1:05 - 1:35 PM

Matt D. Disney

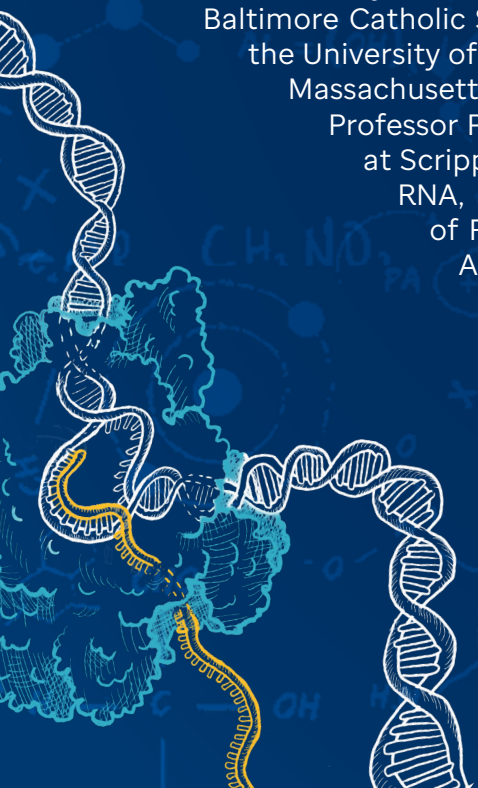
Chair, Department Of Chemistry
Scripps Research Institute

Sequence-based Design of Small Molecules Targeting RNA Structures to Manipulate and Study Disease

One major scientific challenge is to understand biological pathways and to exploit the targets within them for therapeutic development. Coding and non-coding RNAs both directly causes disease, whether by mutation or aberrant expression. Akin to proteins, RNA structure often dictates its function in health or dysfunction in disease. RNA, however, is generally not considered a target for small molecule chemical probes and lead medicines, despite its immense potential. The focus of our research program is uncover fundamental principles that govern the molecular recognition of RNA structures by small molecules to enable design of chemical probes that targeting disease relevant RNA structures to perturb and study their function. In this talk, I will describe using evolutionary principles to identify molecular recognition patterns between small molecules and RNA structures by studying the binding of RNA fold libraries to small molecule libraries. The resultant, privileged interactions are computationally mined across the human transcriptome to define cellular RNAs with targetable structure. Such an approach has afforded bioactive interactions that have uncovered new biology, where the small molecules bind to functional structures within a target RNA. Recently, we have devised a strategy to imbue biologically silent RNA-small molecule interactions with cellular activity. In particular, chimeras comprising an inactive small molecule and ribonuclease recruiter trigger targeted degradation of disease-causing RNAs. These degraders affect the biology of RNA in specific ways in cells and in mouse models of various diseases and can rationally reprogram protein-targeted medicines for RNA.

About the Speaker

Matthew Disney and is a native of Baltimore, Maryland. He received his early schooling in the Baltimore Catholic School System, His B.S. from the University of Maryland, and his Ph.D. from the University of Rochester in Physical Chemistry. He completed postdoctoral training at the Massachusetts Institute of Technology and the Swiss Federal Institute of Technology in Professor Peter H. Seeberger's lab. Matt is a Professor in the Department of Chemistry at Scripps Research. His laboratory works in the area of small molecule targeting of RNA, addressing fundamental questions surrounding the molecular recognition of RNA folds by small molecules to study problems of biomedical importance. Applications have included development of sequence-based design of small molecules, on-site drug synthesis in disease-affected cells, understanding the biology of coding and non-coding RNAs, and interfacing RNAs with quality control machinery, the latter including small molecule degraders and chimeric degrading compounds. The lab's research has garnered various awards including the ACS Nobel Laureate Signature Award for Graduate Education in Chemistry (with Alicia Angelbello), the Scripps Florida Mentor of the Year, the Sackler Prize in the Physical Sciences, Barry Cohen Award in Medicinal Chemistry, NIH Director's Pioneer Award, the Tetrahedron Young Investigator Award, the David W. Robertson Award in Medicinal Chemistry, and others.



David D. Moore

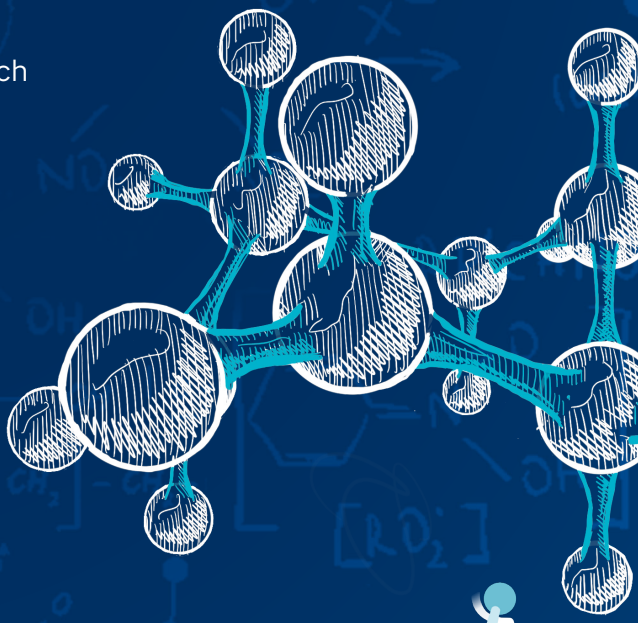
Professor in the Department of Molecular and Cellular Biology
Baylor College of Medicine

Regulation of Liver Energy Balance by Nutrient-sensing Nuclear Receptors

The nuclear receptors PPARα (encoded by NR1C1) and farnesoid X receptor (FXR, encoded by NR1H4) are activated in the liver in the fasted and fed state, respectively. PPARα activation induces fatty acid oxidation, while FXR controls bile acid homeostasis, but both nuclear receptors also function coordinately to control other metabolic pathways relevant to liver energy balance, including fatty acid oxidation and gluconeogenesis in the fasted state and lipogenesis and glycolysis in the fed state. These receptors have mutually antagonistic impacts on another pathway very relevant to energy balance, autophagy, which is induced by PPARα but suppressed by FXR. Autophagy repletes the intracellular pool of amino acids by recycling, but the process of secretion depletes the same pool. Because 40% of the mRNA in hepatocytes encodes secreted proteins and approximately 10% of the ATP used in the cell goes to their translation, secretion is very relevant to hepatic energy balance. Through both transcriptomic and proteomic profiling, we have found that de novo protein synthesis, particularly in the liver secretome and exosomal proteome, is directly suppressed by PPARα but induced by FXR. This discovery is linked to human development by previous studies that demonstrated a striking deficiency in bile acid levels in malnourished mice and also in malnourished children. Further results confirm that the fasting responsive PPARα is activated in undernourished mouse models. We have found that multiple hepatic targets of PPARα and FXR are dysregulated in chronic undernutrition. This includes repression of liver secretome components in the complement and coagulation cascades, and undernourished mice show blood coagulation defects that are also observed in malnourished human subjects. We conclude that PPARα and FXR function coordinately to integrate liver energy balance.

About the Speaker

Dr. David D. Moore is currently Robert R. P. Doherty Jr. - Welch Professor in the Department of Molecular and Cellular Biology at Baylor College of Medicine (BCM), and also Professor in the Departments of Medicine and Molecular and Human Genetics. Before coming to BCM in 1997, he was Assistant and then Associate Professor in the Department of Genetics at Harvard Medical School, and also Assistant and then Associate Molecular Biologist in the Department of Molecular Biology at Massachusetts General Hospital. The focus of his research is hormone receptors, particularly a number of nuclear hormone receptors that regulate diverse metabolic pathways and processes in the liver.



Dorothee Kern

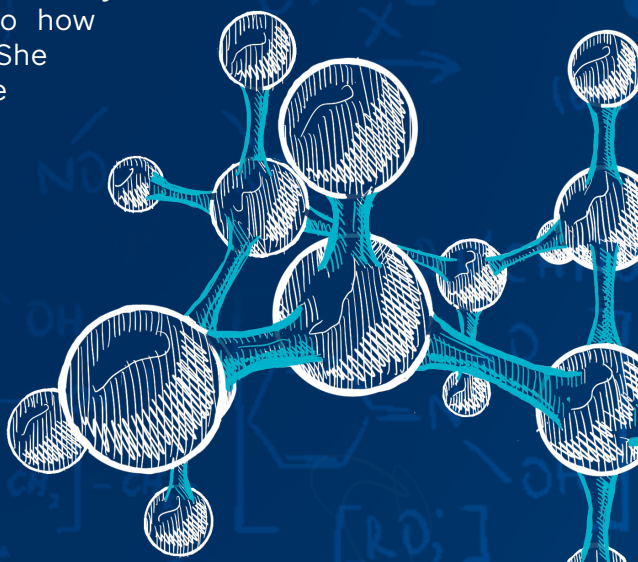
HHMI/ Brandeis University, Dept. of Biochemistry

Protein Dynamics at the Heart of New Cancer Drug Design Approaches

Protein kinases have been the number one cancer drug targets of the 21st century. The drug development has been focused on the active site although this the most conserved part of kinases, creating an uphill battle for selective inhibitors. Why did nature evolve about 500 different protein kinases in humans and what differentiates them? Modern human protein kinases differ in their allosteric regulation, a feature that evolved to enable sophisticated signaling. Therefore, we describe here the power and advantages of taking advantage of differential regulation for developing allosteric modulators (inhibitors and activators) with extreme specificity and high affinity. I will describe that the dynamic protein ensemble description is at the heart of the natural function and regulation of proteins, but also in drugging them. One of the major obstacles in cancer treatment is the development of drug resistance. Findings about surprising mechanisms behind drug resistance mutations in cancer patients, and novel approaches to overcome drug resistance in future rational drug design will be presented. General lessons learned here on kinases and phosphatases can be applied to other enzyme classes.

About the Speaker

Dorothee Kern is a Professor of Biochemistry at Brandeis University and the director of the graduate program in biophysics and biochemistry. She has been an investigator of the Howard Hughes Medical Institute since 2005. Dorothee strives to understand how proteins function by understanding how they move at atomic resolution. She uses biophysical analytical methods, such as nuclear magnetic resonance (NMR) and x-ray, to analyze protein dynamics. She has followed the high-speed motion of enzymes during biocatalysis and allosteric regulation, providing unexpected insights into how conformational change are essential for biological reactions. She has recently expanded the concept of protein motion to the evolution of proteins over billions of years by reconstructing evolutionary trajectories in vitro. Dorothee pursues a new vision of protein dynamics and allosteric networks at the heart of improved drug design, is founder of Relay Therapeutics and MOMA Therapeutics with the mission of exploiting protein dynamics for expanding therapeutics. She received her BS, MS and PhD in biochemistry from Martin Luther University in Halle, Germany. Before moving to California for her post-doc at UC Berkeley and the Lawrence Berkeley National Laboratory, Dorothee was captain of the German National Basketball team for many years and won an MVP award. In 1998, she joined the faculty of Brandeis University and transferred her leadership skills from the basketball court to the lab.



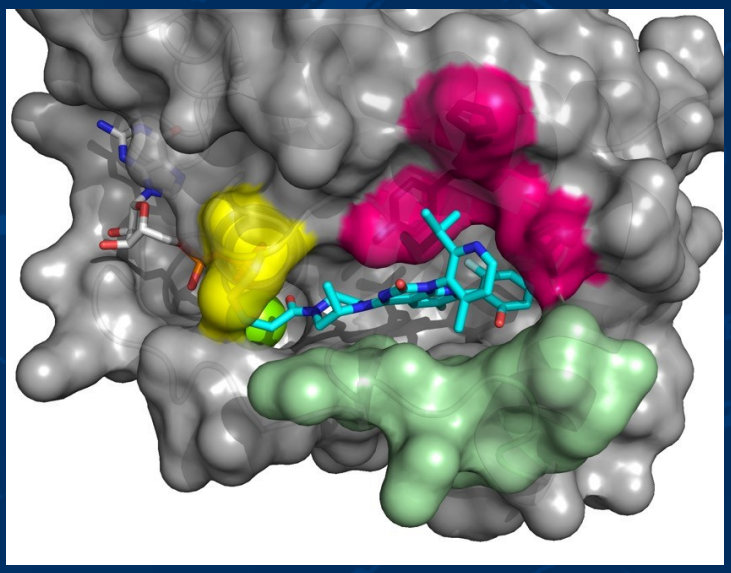
3:05 - 3:35 PM

Raymond J. Deshaies

Senior Vice President of Global Research
Amgen, Inc.

The Awesome Power of Synthetic Organic Chemistry in Drug Development

Chemistry is at the heart of drug development. In the early days of the industry, chemistry was the only game in town. New medicines were discovered in natural sources and either purified from the source or synthesized in a laboratory. The advent of biologics started a new era, in which medicines were produced in cells grown in bioreactors. We are now in a third phase that is increasingly characterized by hybrid modalities. In my presentation I will review 3 types of medicines from our clinical pipeline that highlight the diverse contributions of chemistry to drug discovery. The first, AMG 193, an MTA-cooperative inhibitor of PRMT5, represents what modern medicinal chemistry can deliver when coupled with sophisticated DNA-encoded library screening technology. The second, olpasiran, is also a chemically synthesized molecule – an siRNA that targets the LPA mRNA and brandishes a phalanx of chemical modifications including a triantennary N-acetylgalactosamine to facilitate its uptake by liver cells. The third is a hybrid molecule comprising a conventional monoclonal antibody against glucose insulinotropic peptide receptor (GIPR) covalently conjugated to two molecules of a synthetic derivative of glucagon-like peptide 1 (GLP-1). Together, these molecules illustrate the different ways in which chemistry is deployed in the production of drugs and highlight potential opportunities for the future.

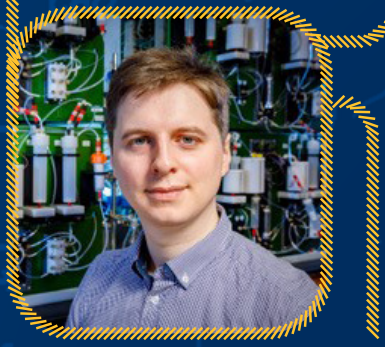


About the Speaker

Prior to joining Amgen, Deshaies served as a professor at the California Institute of Technology (Caltech) and an executive officer in Caltech's Division of Biology and Biological Engineering. He was also an investigator at the Howard Hughes Medical Institute. He has published over 150 papers on various subjects including discoveries of Sec61 translocon, cullin–RING ubiquitin ligases, and proteolysis-targeting chimeric molecules (Protacs). In addition to his academic work, Deshaies co-founded Proteolix in 2003. In 2011, he co-founded Cleave Biosciences. Deshaies holds a bachelor's degree in biochemistry from Cornell University and a Ph.D. in biochemistry from the University of California, Berkeley. He is also a member of the National Academy of Sciences, and American Academy of Arts and Sciences.

Daniel Blair

Newst Member, St. Jude Chemical Biology and Therapeutics
Former: University of Illinois at Urbana-Champaign

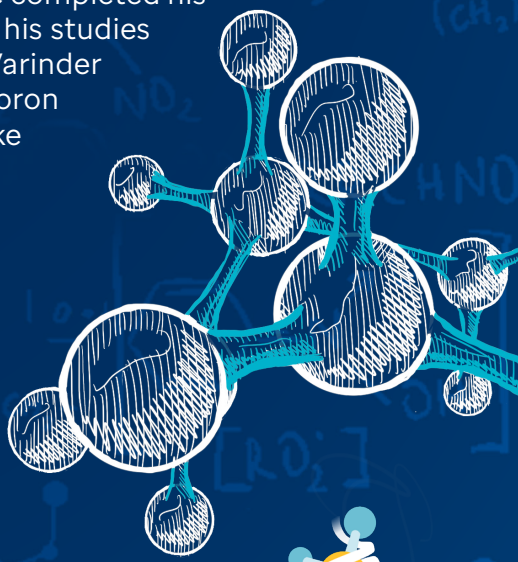


Modularized Molecule Making

Small molecules created by nature (natural products) possess extraordinary functional potential, and have led to many transformative human medicines (artemisinin, penicillin, Taxol, and Lipitor). These exceptional functional properties result from the highly complex arrangement of functional groups in 3D-space that many natural products possess. Unfortunately, despite nearly 200 years of important progress in the field of small molecule synthesis, the methods available for synthesizing complex natural products and their derivatives are typically too slow for practical drug discovery and development. Fully automated synthetic chemistry would substantially change the field by providing broad on-demand access to these complex small molecules. However, the reactions that can be run autonomously are still limited. Automating the stereospecific assembly of Csp3–C "3D" bonds would expand access to many important types of functional organic molecules - including natural products. Previously, methyliminodiacetic acid (MIDA) boronates were used to orchestrate the formation of Csp2–Csp2 "2D" bonds and were effective building blocks for automating the synthesis of many small molecules, but they were incompatible with Csp3–Csp2 and Csp3–Csp3 "3D" bond-forming reactions. Today we will describe how hyperconjugative and steric tuning collaborate to create a new class of tetramethyl N-methyliminodiacetic acid (TIDA) boronates which are stable to these conditions. This enabled Csp3 boronate building blocks to be assembled using automated synthesis, including the preparation of natural products through automated stereospecific Csp3–Csp2 and Csp3–Csp3 bond formation. These findings will enable increasingly complex Csp3-rich small molecules to be accessed via automated assembly.

About the Speaker

Daniel Blair grew up in the North-East of England in Kingston upon Hull, he completed his MSci in Chemistry at The University of Bristol (UK) in 2011. He continued his studies at Bristol with a Ph.D. in Organic Chemistry under the guidance of Prof. Varinder K. Aggarwal FRS focusing on stereoselective organolithium and organoboron chemistry, graduating in 2016. Daniel then moved to the USA to undertake postdoctoral research in automated chemical synthesis with Prof. Martin D. Burke at the University of Illinois at Urbana-Champaign and was awarded a Damon Runyon Cancer Research Foundation postdoctoral fellowship to support his work on automated small molecule synthesis. Daniel will start his independent laboratory at St Jude this Fall in the Department of Chemical Biology & Therapeutics.



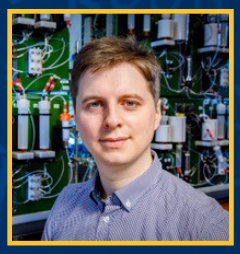
CBT Research Groups

Aseem Ansari

Designing synthetic gene switches for transcription therapy

Hai Dao

Manipulating chromatin to decode epigenetic regulation of gene expression



Daniel Blair

Exploring the frontiers of covalent inhibitors and automated synthesis

Marcus Fischer

Exploring the protein conformational landscape for ligand discovery

Scott Blanchard

Understanding structure-function relationships in complex biochemical systems at the single-molecule scale.

Richard Lee

Discovering new antibiotics and other therapeutics using medicinal chemistry and chemical biology

Taosheng Chen

Deciphering transcriptional regulation of therapeutic responses.

Zoran Rankovic

Medicinal chemistry, targeted protein degradation, CNS drug design

Tommaso Cupido

Chemical targeting of molecular machines

Anang Shelat

Identifying and translating druggable liabilities in pediatric cancers

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