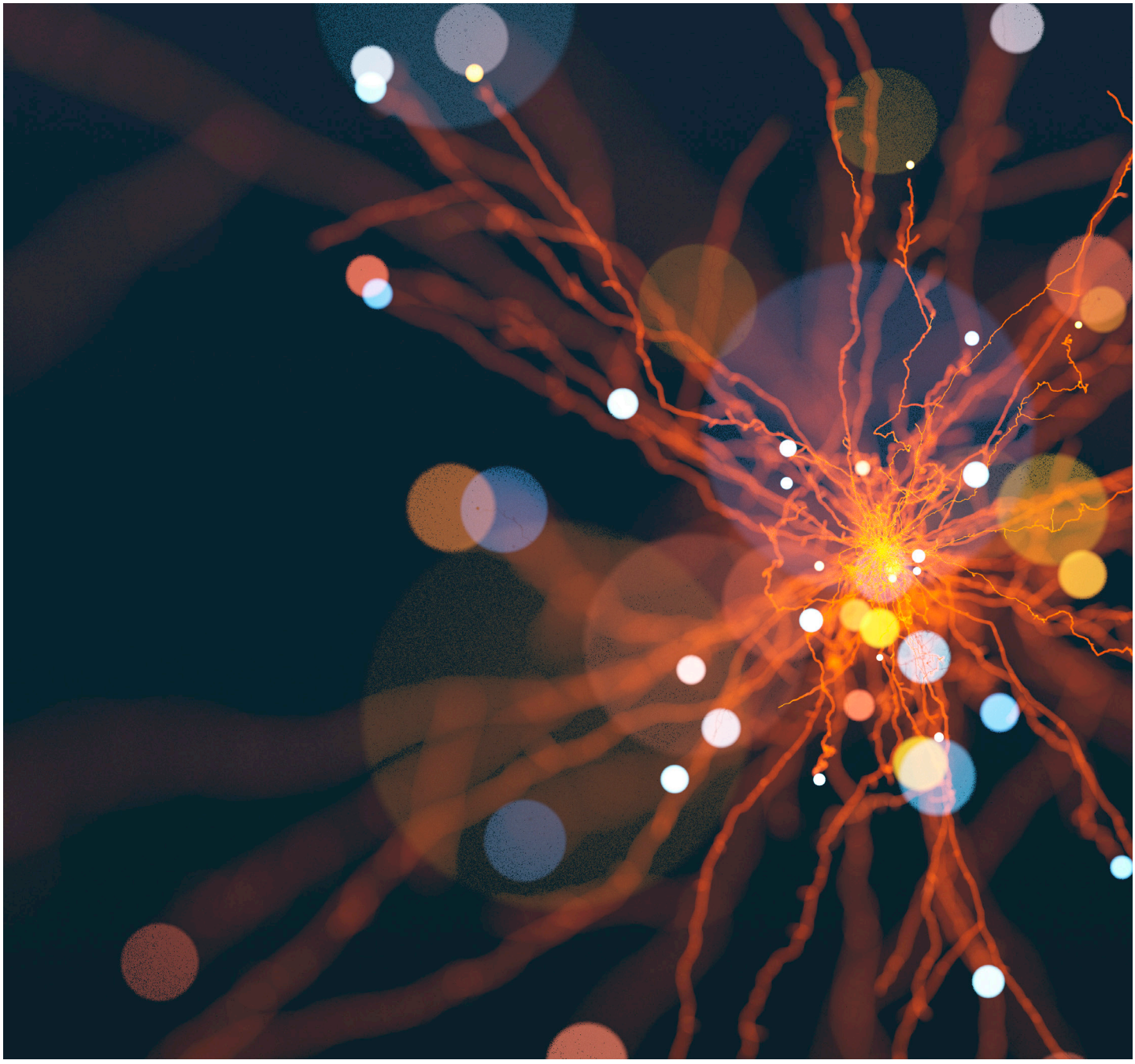
Symposium 2019

RNA: From Biology to Drug Discovery

at Scripps Research



Scripps Research

Schedule

Scripps Research 120 Scripps Way, Jupiter, FL 33458 · Rodney B. Fink Auditorium

Time	Talk Title	Speaker
8:00 - 9:00 am	**Registration check-in + Symposium program pickup** Continental breakfast provided	
9:00 - 9:05 am	**Opening Remarks**	Matthew Disney
Session 1		
9:05 - 9:35 am	**Translating RNA Sequence Into Lead Small Molecule Medicines**	Matthew Disney
9:40 - 10:10 am	**Understanding the Link Between C9Orf72 FTD/ALS and TDP-43**	Leonard Petrucelli
10:15 - 10:45 am	**Nonsense-Mediated mRNA Decay in Health and Disease**	Lynne Maquat
10:45 - 11:00 am	**Coffee Break**	
11:00 - 11:30 am	**Mechanistic Studies on Natural Products that Bind and Alkylate or Cleave Nucleic Acids**	Dale Boger
11:35 - 12:05 pm	**Using the RNA Inside Virus-Like Particles for Unnatural Purposes**	M.G. Finn
12:05 - 1:35 pm	**Lunch and Poster Viewing**	
Session 2		
1:35 - 2:05 pm	**Predicting RNA Structure with Physics and Sequence Comparison**	David Mathews
2:10 - 2:40 pm	**Targeting RNA by Small Molecules: A Perspective From Nature**	Robert Batey
2:45 - 3:15 pm	**RNA Regulation in Repeat Expansion Diseases**	Eric Wang
3:15 - 3:30 pm	**Coffee Break**	
3:30 - 4:00 pm	**Quality Control During Ribosome Assembly**	Katrin Karbstein
4:05 - 4:35 pm	**Algorithms for Predicting RNA Secondary Structure: Making the Most of an Ill-Conditioned Problem**	Michael Zuker
4:35 - 4:45 pm	**Final Remarks**	Matthew Disney

Speaker Abstracts

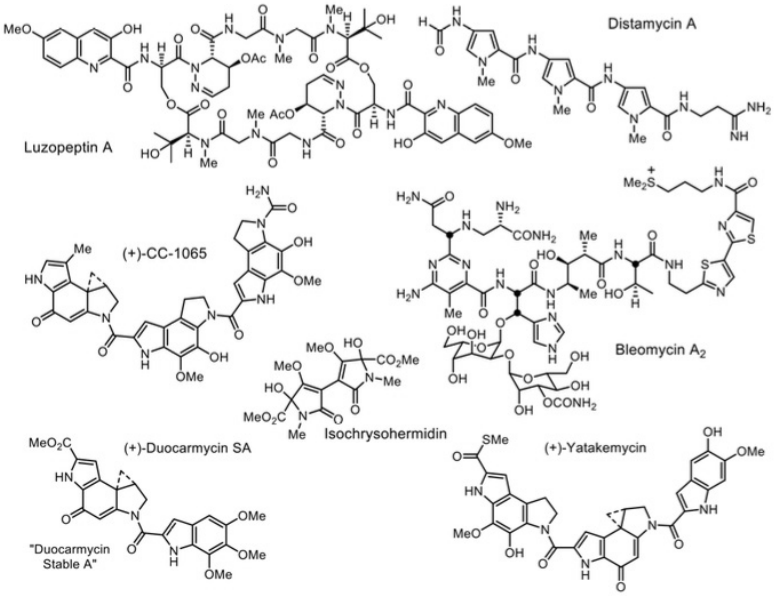
Robert Batey, PhD
The University of Colorado at Boulder

Recent discoveries regarding the extent of pervasive transcription throughout the human genome and its relevance to cellular dysfunction and disease have sparked intense interest in developing therapeutics that target RNA. Despite a few recent successes in developing small molecules that target RNA, the insights into how small molecules can be developed that specifically target an RNA site and affect its cellular function remain sparse. To address this issue, our group has focused on studying natural RNAs that evolved to bind small molecules as part of their biological function. A particularly rich set of small molecule binding RNA elements are *riboswitches*. These are elements generally found within the 5' leader region of bacterial mRNAs that directly interact with cellular metabolites to regulate the message's expression. Effector binding by the receptor (aptamer) domain directs conformational changes within a regulatory domain (expression platform), which informs the expression machinery. Over the past decade, we have solved the crystal structures of a diverse set of riboswitches in complex with their effector ligands and used an array of biophysical, genetic and computational tools to understand how small molecules direct RNA folding pathways that inform the regulatory switch. In this talk, I will summarize these findings and discuss how these insights can be leveraged to develop new RNA targeting therapeutics.

Dale Boger, PhD
Scripps Research

A summary of studies of natural products that exhibit their biological activity through sequence selective binding and alkylation or cleavage of nucleic acids will be presented. The underlying molecular basis of their nucleic acid recognition, the source of their subsequent reactivity, and the ramifications will be highlighted for the duocarmycins, yatakemycin, CC-1065, and bleomycin related natural products.

Natural Product Solutions to the Sequence Selective Recognition of Nucleic Acids



Matthew Disney, PhD
Scripps Research

About 80% of our genome is transcribed into RNA and only about 2% is translated into protein. Yet, drug discovery focuses almost exclusively on targeting protein. A major challenge in medical science has been exploiting targets for drug development. Our programmatic focus is on developing technologies to decipher which cellular RNAs are "druggable" targets for small molecules and which small molecules can target them. Here, we will describe advances in the area of Small Molecules Interacting with RNA (SMIRNAs), including a sequence-based small molecule rational design tool dubbed Inforna. It has enabled the design of SMIRNAs against RNAs that cause hard-to-treat cancers and incurable genetically-defined diseases that have no known treatment by scanning for druggable pockets across human RNA sequence. We will describe these compounds and their implications advancing lead medicines and also as chemical probes to understand previously unknown RNA biology. We will also describe the development of approaches that allow for targeted degradation of RNAs in cells and animals by using SMIRNAs. For example, we can recruit endogenous cellular nuclease to cleave RNAs selectively and sub-stoichiometrically in cells and animals. There is great opportunity to capture the decades of discovery of RNA biology to deliver small molecule chemical probes and lead medicines targeting RNA. Although RNA has been thought to not be broadly targetable with organic ligands, these advances suggest that this needs reassessment.

M.G. Finn, PhD
Georgia Tech University

When expressed in any living cell, capsid proteins from RNA viruses trap RNA. If not part of an active viral infection, as in the production of non-replicative virus-like particles, this RNA can be of many different types. When bacterial in origin, this RNA is sensed by the mammalian immune system; when mammalian in origin, this RNA can be delivered and transcribed, albeit usually with poor efficiency. We are beginning to explore other uses for this polyanionic material inside easily-functionalized protein shells, primarily focused on properties of binding and release of other molecular cargo. In addition, our current best practices for performing azide-alkyne cycloaddition ligation to RNA and DNA will be described.

Katrin Karbstein, PhD
Scripps Research

Changing the number or composition of ribosomes is linked to a growing number of diseases, which share a predisposition to develop specific forms of cancer. Conversely, it is becoming apparent that cancer cells also change the number and composition of their ribosomes, and that this is linked to a poor prognosis. Thus, taken together, these two observations underline the importance of mechanisms to ensure that ribosomes are correctly and completely assembled. Ensuring that only fully and correctly matured ribosomes are released into the translating pool is important, as immature ribosomes can translate, but perturb translational fidelity, protein homeostasis and do not support cell viability. Using a combination of biochemical experiments, genetic and genomic approaches, we have uncovered a checkpoint, established by the endonuclease Nob1, which produces the mature 3'-end of 18S rRNA and its binding partner, Pno1, which prevents release of immature ribosomes into the translating pool. This checkpoint is regulated by the cancer-associated kinase Rio1, which releases these proteins *after* rRNA maturation. Bypass of this checkpoint using self-releasing mutants in Nob1 and Pno1 leads to the release of immature ribosomes into the translating pool, thus demonstrating the importance of this checkpoint in restricting translation to mature 40S ribosomes. We are currently extending this work by testing a hypothesis that this checkpoint also allows for the correction of mistakes

Katrin Karbstein (continued)

during maturation, eliminating miscleaved RNA by allowing them to re-ligate and giving them another chance at correct cleavage. Consistent with this model, we find mis-processed RNAs in checkpoint-bypass mutants. This is the first evidence of error correction during rRNA processing, analogous to the correction of mistakes during DNA replication, tRNA charging and translation.

David Mathews, MD, PhD
University of Rochester Medical Center

RNA structure is hierarchical. The primary structure is the sequence of nucleotides. The secondary structure is the set of canonical (AU, GC, and GU) base pairs. The tertiary structure is the three dimensional position of the atoms and the additional intramolecular contacts that mediate the fold. The Mathews lab develops methods to predict both RNA secondary structure and tertiary structure. In this talk, I will introduce nearest neighbor parameters for estimating folding stability of secondary structures and dynamic programming algorithms that predict secondary structure. The accuracy of structure prediction can be dramatically improved using additional information provided by experimental mapping experiments or sequence comparison. I will present new work in our lab to compare sequences to model conserved secondary structures. We developed a new method, called TurboFold, which is able to rapidly refine both predicted secondary structures using sequence comparison and sequence alignments using the structure information. I will also talk about new work to model RNA folding stability using molecular mechanics and 3D models. We used umbrella sampling to estimate the unfolding free energy change differences for three stem-loop structures, and we found chemically accurate agreement with experiments.

Lynne Maquat, PhD
University of Rochester Medical Center

Much progress has been made on how nonsense-mediated mRNA decay (NMD), which we first described for humans in 1981, controls the quality of gene expression by detecting and rapidly degrading aberrant mRNAs that contain a premature termination codon. Our studies of NMD have led to the discovery of the pioneer round of translation, the post-splicing "mark" on newly synthesized mRNAs – later named the exon-junction complex (EJC) in a collaboration with Melissa Moore – the mechanistically related and competing Staufen-mediated mRNA decay pathway, including new roles for SINEs, and most recently a microRNA decay pathway. We tracked individual cellular transcripts in collaboration with Rob Singer to confirm our results from the mid-1990's indicating that NMD for a number of mRNAs occurs on the cytoplasmic side of the nuclear envelope. Our data provide explicit evidence that proteins acquired by newly synthesized mRNAs in the nucleus, including the cap-binding protein CBP80 and constituents of the EJC, are critical for mRNA quality control via translation in the cytoplasm. We have also described the molecular mechanism for how NMD targets are discriminated from other transcripts: the central NMD factor – the ATP-dependent RNA helicase UPF1 – preferentially associates with mRNA 3'- untranslated regions (3' UTRs) in a way that correlates with the presence of a 3' UTR EJC or 3' UTR length and/or structure. Importantly, NMD also targets ~10% physiologic mRNAs that are key to maintaining cellular homeostasis in a changing environmental milieu. For example, we reported that a sufficient level of DNA damage induced by commonly used frontline chemotherapeutics inhibits NMD by triggering the caspase-mediated cleavage of sub-stoichiometric amounts of UPF1, thereby upregulating the half-lives of mRNAs that include those encoding proteins promoting apoptosis. Notably, the modest inhibition of NMD promotes but is not sufficient for programmed cell death. These and other results will be discussed.

Leonard Petrucelli, PhD
Mayo Clinic, Jacksonville

A G_4C_2 hexanucleotide repeat expansion in an intron of the gene *C9orf72* is the most common known genetic cause of amyotrophic lateral sclerosis and frontal temporal dementia (c9FTD/ALS). A remarkably similar TG_3C_2 repeat expansion is associated with spinocerebellar ataxia type 36 (SCA36). Both expansions are widely expressed, form RNA foci, and can undergo repeat-associated non-ATG (RAN) translation to form similar dipeptide repeat proteins. And yet, these diseases are characterized by the degeneration of distinct subsets of neurons. We have found that the expression of these repeat expansions in mice is sufficient to recapitulate the unique features of each disease, including this selective neuronal vulnerability. Furthermore, only the expanded G_4C_2 repeat induces the formation of aberrant stress granules and ultimately pTDP-43 inclusions, supporting the hypothesis that these features are mechanistically linked. Overall our results highlight the importance of specific RNA-mediated toxicity in these diseases and shed light on the question of selective neuronal vulnerability in human disorders.

Eric Wang, PhD
University of Florida

There are over 30 microsatellite repeat expansion diseases, many with neuromuscular, neurological, and neurodegenerative features. Some are characterized by aberrant silencing of gene loci, and others by production of toxic polypeptide repeats. Myotonic Dystrophy is one in which production of toxic RNA repeats has been demonstrated to be a key driver of disease pathology via sequestration of RNA binding proteins. Some of these proteins, including the Muscleblind-like family of splicing factors, play key roles in both the nucleus and cytoplasm of muscle and neurons. The somatic instability of repeats in these tissues yields a dynamic landscape in which molecular, cellular, and physiological features exist along a spectrum. Fully understanding the consequences of this instability has helped uncover new biology and reveal effective approaches for therapy.

Michael Zuker, PhD
Rensselaer Polytechnic Institute

With a simplified model of the three dimensional structure of single-stranded RNA, it is possible to assign free energies to arbitrary conformations using parameters derived by physical chemists. Practical algorithms can be formulated to predict minimum and close to minimum free energy conformations as well as ensemble properties such as base pair probabilities and melting profiles. Given the model, these computations are exact. However, the problem itself is ill-conditioned in the sense that solutions are sensitive to small fluctuations in energy parameters and slight changes in nucleic acid composition. These problems can be mitigated by computing average properties, by adding auxiliary information to constrain solutions and by accepting that some of the uncertainty might be genuine. For over 25 years, visual inspection of “energy dot plots” has been used to assign a subjective measure to the reliability of predictions. More recently, the entropy of the Boltzmann distribution of all possible secondary structures assigns a numerical value to the propensity of an RNA to fold in a “well-defined” manner. Low entropy is associated with better predictions, whereas high entropy indicates either structural plasticity or the failure of the thermodynamic model to be useful for certain RNAs. Systematic *in silico* mutations of an RNA have shown that particular single base changes can cause a large change in entropy together with a significant change in secondary structure.

Speaker Biographies

Robert Batey, PhD

Robert Batey is a Professor of Biochemistry at the University of Colorado, Boulder, where he has been since 2001. He received his PhD degree in Biology from the Massachusetts Institute of Technology in 1997 with Professor Jamie Williamson and was a Jane Coffin Childs postdoctoral fellow at Yale University with Professor Jennifer Doudna between 1997 and 2001. The Batey laboratory seeks to understand how structured RNA elements directs gene expression. In 2004, his research team was the first to reveal the structural basis for small molecule binding by a naturally-occurring regulatory element called a riboswitch. These sequences, frequently found in bacterial mRNAs, directly bind a small molecule effector to an "aptamer" that directs a structural switch that in turn informs the expression machinery. Since these first insights, the Batey laboratory has worked extensively on the structural and mechanism of spectrum of riboswitches that bind diverse small molecules including guanine, S-adenosylmethionine, lysine, tetrahydrofolate, vitamin B12, and the purine biosynthetic intermediate ZMP. Using a combination of structural, biochemical and cell-based approaches, the Batey laboratory has provided many of the key insights into how small molecule binding by RNA can be harnessed to regulate mRNA expression. More recently, he has sought to leverage our knowledge of natural aptamers to develop new approaches to evolving synthetic aptamers in vitro for cellular applications. We have shown that certain RNA architectures can act as privileged scaffolds, capable of hosting novel binding activities and retain robust intracellular function. These efforts are ongoing with the goal of developing a broad range of synthetic aptamers for a range of diagnostic and therapeutic applications. In addition, he has recently developed the cobalamin riboswitch into a new tool for imaging RNA in live mammalian cells called "Riboglow."

Dale Boger, PhD

Dale Boger received his BSc in chemistry from the University of Kansas (1975, with highest distinction and honors in chemistry) and PhD in chemistry from Harvard University (1980) under the direction of E. J. Corey and supported by an NSF fellowship. He returned to the University of Kansas as a member of the faculty in the Department of Medicinal Chemistry (1979-1985), moved to the Department of Chemistry at Purdue University (1985-1991), and joined the faculty in the newly created Department of Chemistry at The Scripps Research Institute (1991-present) as the Richard and Alice Cramer Professor of Chemistry. From 2012-2018, he served as the Chairman for the Department of Chemistry. Professor Boger is internationally recognized for his work in organic synthesis, heterocyclic chemistry, medicinal chemistry, natural products total synthesis and their biological characterization, synthetic methodology development, and chemical biology, and has made seminal contributions to discovering new therapeutic targets (e.g., FAAH, serine hydrolases), improving the glycopeptide antibiotics, and the understanding of DNA-drug interactions of naturally occurring antitumor-antibiotics.

Matthew Disney, PhD

Matthew Disney is a Full Professor of Chemistry at the Florida campus of Scripps Research with a joint appointment in Neuroscience. Since starting his independent career in 2005, Prof. Disney has focused his research efforts on the selective recognition of RNA by small molecules to show that RNA is indeed broadly druggable, i.e. outside of the bacterial ribosome. Towards this end, he has pioneered synergistic computational and experimental approaches to tackle this difficult molecular recognition problem. In particular, his group developed a sequence-based rational design approach to identify small molecules that target RNA, dubbed Inforna. Inforna finds druggable RNA motifs within the human transcriptome and lead compounds to target them. The lead identification strategy leverages the results of an experimental library-versus-library screen, developed by Prof. Disney and colleagues, named Two-Dimensional Combinatorial Screening (2DCS). The 2DCS approach rapidly selects privileged small molecule-RNA motif binding partners by studying the binding of libraries of small molecules to libraries of RNA structural elements. The Disney laboratory also developed the first approaches to validate the cellular RNA targets of small molecules. These approaches, Chem-CLIP and RiboSNAP, allow for profiling RNAs that bind small molecules in cells via cross-linking or cleavage, respectively. Prof. Disney has authored over 140 publications and has been cited almost 8,000 times. Based on this work, Prof. Disney co-founded Expansion Therapeutics, Inc., a biotechnology company focused on delivering medicines to patients with the most urgent needs and the least treatment options. Prof. Disney's work has garnered many awards, including the NIH Director's Pioneer Award, the Tetrahedron Young Investigator Award, the Eli Lilly Award in Biological Chemistry from the American Chemical Society, the Barry Cohen Prize (awarded by the Medicinal Chemistry section of the Israel Chemical Society and Teva Pharmaceutical Industries), BioFlorida's Weaver H. Gaines "Entrepreneur of the Year" Award, and the Raymond and Beverley Sackler International Prize in the Physical Sciences. He serves on both the Scientific Advisory Board of the RNA Institute at The University at Albany and the Elsevier Tetrahedron Journal Board. He is Editor for the Americas for Bioorganic and Medicinal Chemistry Letters.

M.G. Finn, PhD

M.G. Finn received a BSc degree in Chemistry from Caltech in 1980, and a PhD degree in 1986 from MIT working with Prof. K.B. Sharpless, followed by an NIH postdoctoral fellowship with Prof. J.P. Collman at Stanford University. He joined the faculty of the University of Virginia in 1988, where his group studied and developed a variety of transition metal-mediated synthetic methods. Prof. Finn moved to the Department of Chemistry and The Skaggs Institute for Chemical Biology at The Scripps Research Institute in 1998, and then to the School of Chemistry & Biochemistry and the School of Biological Sciences at the Georgia Institute of Technology in 2013. He assumed the chairmanship of the former department in 2014. Prof. Finn's current interests include the use of virus particles as molecular and catalytic building blocks for vaccine and functional materials development, the discovery of click reactions for organic and materials synthesis, polyvalent interactions and advanced linker technologies in drug targeting, and the use of evolution for the discovery of chemical function. He is currently the Chief Scientific Officer of the Pediatric Technology Center, a joint effort of Georgia Tech, the Emory University Medical School's Department of Pediatrics, and Children's Healthcare of Atlanta, to bring new science and engineering to the aid of pediatric medicine. He holds the James A. Carlos Family Chair for Pediatric Technology. Professor Finn was the first recipient of the annual Scripps Outstanding Mentor

M.G. Finn (continued)

Award, a 2017 Arthur C. Cope Scholar award, and is Editor-in-Chief of the journal ACS *Combinatorial Science*.

Katrin Karbstein, PhD

Katrin Karbstein obtained her PhD in Biochemistry from Stanford University, where she studied with Professor Daniel Herschlag how RNA enzymes promote catalytic reactions, focusing in particular on the role of conformational transitions. After obtaining her PhD, she moved to the University of California at Berkeley, where she worked under the mentorship of Professor Jennifer Doudna. After completing her postdoctoral studies in 2006, Dr. Karbstein obtained a faculty position at the University of Michigan in Ann Arbor. In 2010 she was recruited to the recently established The Scripps Research Institute in Jupiter, FL, where Dr. Karbstein first joined the Cancer Biology Department. Dr. Karbstein is currently a tenured Associate Professor in the Department of Integrative Structural and Computational Biology, where her lab studies how ribosomes are assembled within cells, how this assembly is both regulated and quality controlled, and how a breakdown of this process leads to diseases. Her scientific work has been recognized with an HHMI Faculty Scholar award. Besides her laboratory research, Dr. Karbstein is the PI of the NSF-funded summer undergraduate research program "SURFing the Interface between Chemistry and Biology" at Scripps Research, Florida, and a member of the Scripps Research graduate admission committee. Her former students are in the top graduate and postdoctoral programs in the country, or have taken up faculty positions at Emory University, Trinity College, Eckerd College, Boston College, and Keystone College, in addition to leadership positions in the biotech industry. In addition to her work, Dr. Karbstein enjoys spending time with her two daughters, age 13 and 15.

David Mathews, MD, PhD

David Mathews is a Professor of Biochemistry & Biophysics at the University of Rochester Medical Center, where he established his research group in 2004. His group develops computational methods to model RNA structure. They work to improve RNA secondary structure prediction and to model the all-atom structure and dynamics of RNA. Dr. Mathews received his undergraduate degree in Physics from the University of Rochester. He also completed medical and graduate school at the University of Rochester. He received his PhD in Chemistry for thesis work with Professor Doug Turner, focused on predicting RNA secondary structure. Dr. Mathews completed a post-doc with David Case at the Scripps Research Institute, San Diego, CA, to work on all-atom modeling of RNA. Dr. Mathews was an Alfred P. Sloan foundation fellow and was highlighted by Genome Technology as one of "Tomorrow's PIs".

Lynne Maquat, PhD

Lynne Elizabeth Maquat is the J. Lowell Orbison Endowed Chair and Professor of Biochemistry & Biophysics in the School of Medicine and Dentistry, Director of the Center for RNA Biology, and Chair of Graduate Women in Science at the University of Rochester, Rochester, NY. After obtaining her PhD in Biochemistry from the University of Wisconsin-Madison and undertaking post-doctoral work at the McArdle Laboratory for Cancer Research, she joined Roswell Park Cancer Institute before moving to the University of Rochester. In 1981, Professor Maquat discovered nonsense-mediated mRNA decay (NMD) in mammalian cells and, subsequently while elucidating the mechanism of NMD, the exon-junction complex (EJC) and how the EJC marks mRNAs for a quality-control "pioneer" round of protein synthesis. She also discovered Staufen-mediated mRNA decay, which mechanistically competes with NMD and, by so doing, creates new roles for short interspersed elements and long non-coding RNAs. Additional current interests include microRNA decay, mechanisms by which cells utilize NMD and SMD to adapt to developmental and environmental changes, how transposable elements have been co-opted by cells to regulate gene expression, functional links between transcription factors and RNA-binding proteins, and developing therapeutics by targeting RNA. Professor Maquat is an elected Fellow of the American Association for the Advancement of Science (2006), and an elected Member of the American Academy of Arts & Sciences (2006), the National Academy of Sciences (2011), and the National Academy of Medicine (2017). She was a Batsheva de Rothschild Fellow of the Israel Academy of Sciences & Humanities (2012-2013) and has received the William C. Rose Award from the American Society for Biochemistry & Molecular Biology (2014), a Canada Gairdner International Award (2015), the international RNA Society Lifetime Achievement Award in Service (2010) and in Science (2017), the Vanderbilt Prize in Biomedical Science (2017), the Federation of American Societies for Experimental Biology (FASEB) Excellence in Science Award (2018), the Wiley Prize in Biomedical Sciences (2018), and International Union of Biochemistry and Molecular Biology Medal (2019).

Leonard Petrucelli, PhD

Leonard Petrucelli is a Ralph B. and Ruth K. Abrams Professor and enterprise chair of the Department of Neuroscience at Mayo. Dr. Petrucelli earned his Bachelor of Science degree at Barry University, Miami, and his PhD degree in molecular and cellular biochemistry at Loyola University and the Stritch School of Medicine, Chicago. He came to Mayo Clinic's Florida campus as a research fellow in 2000 and joined the neurosciences research staff two years later. Dr. Petrucelli and his research team are at the forefront of their field, researching the cellular mechanisms that cause neurodegeneration in Alzheimer's disease, amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease, frontotemporal dementia (FTD) and more recently, movement disorders and stroke. By combining expertise in drug discovery, cell biology and induced pluripotent stem cell (iPSC) modeling, his lab aims to develop therapies and biomarkers for the treatment of diseases characterized by abnormal protein aggregation. Dr. Petrucelli's team recently discovered a new therapeutic target and biomarker with the aim of improving the diagnosis and prognosis for patients suffering from FTD and ALS. His team's research has been published in top tier journals including Science, Nature Medicine, Nature Neuroscience, Neuron, Journal of Clinical Investigation and Annals of Neurology.
Dr. Petrucelli is principal investigator for several grants funded by the National Institutes of Health (NIH) including R35 and is director of two funded NIH programs focused on c9orf72

Leonard Petrucelli (continued)

and Tau Center without Walls. He serves on the Scientific Advisory Board of Science Translational Medicine. He is also the Chief Scientific Advisor to the Target ALS Foundation. Lastly, he was recently appointed as vice-chair to the Florida Alzheimer's Disease Research Grant Advisory Board.

Eric Wang, PhD

Eric Wang received his B.A. in Biochemistry from Harvard College and his PhD from the Harvard-MIT Division of Health Sciences and Technology in Medical Engineering/Medical Physics with a focus on Bioinformatics and Integrative Genomics. He performed his graduate work with Christopher Burge and David Housman, developing and applying experimental and computational methods to studying alternative splicing across tissue transcriptomes (cited >2500 times), quantitating RNA processing events, and uncovering a role for Muscleblind-like proteins in regulating RNA localization. Following receipt of an NIH Director's Early Independence Award, he launched his independent research group at the Koch Institute for Integrative Cancer Research at MIT. He is currently an Assistant Professor in the Center for Neurogenetics and Department of Molecular Genetics and Microbiology at the University of Florida. He has received multiple grants from NIH, MDA, and the Myotonic Dystrophy Foundation, and recently received a Ben Barres Neurodegeneration Career Acceleration Award from the Chan-Zuckerberg Initiative. Dr. Wang's family is affected by myotonic dystrophy, and outside of academic research, Dr. Wang has been involved with the Myotonic Dystrophy Foundation and the Muscular Dystrophy Association, and serves on the board of the Promise to Kate Foundation, helping these organizations to raise awareness and funding for muscle disease research.

Michael Zuker, PhD

Michael Zuker spent most of his career developing and applying software for protein and nucleic acid sequence analysis. He is best known for his work in RNA and DNA secondary structure prediction. His algorithms and software were later extended to simulate nucleic acid hybridization and melting profiles. He has offered an RNA and DNA folding web service since 1995 and web based applications for nucleic acid hybridization and melting curve predictions since 2005. The current web server has been running at the University at Albany (NY) since November 2010. His biology related educational activities include developing and teaching an original bioinformatics course at Rensselaer, and participating in both a Chautauqua short course in bioinformatics for college teachers and an intensive bioinformatics course at the University of Michigan for working professionals. Dr. Zuker was a research officer at the National Research Council of Canada from 1974 to 1994. From 1994 to 2000 he was an associate professor of Biomedical Computing at Washington University in St. Louis, and in 2000 he became a professor of Mathematical Sciences at Rensselaer Polytechnic Institute. He was an adjunct professor in the RNA Institute at U. Albany from 2011 to 2017 and retired from Rensselaer at the end of 2016. He currently serves on the Scientific Advisory Board of Expansion Therapeutics, Inc.

Our Hosts

The Disney Laboratory

The Disney Group is focused on developing rational and predictable approaches to design highly selective therapeutics from only genome sequence. One of the major articulations of the utility of genome sequencing efforts has been in advancing patient-specific therapies, yet such developments have been only sparsely reported. We accomplish this lofty goal by using advancements in annotating RNA structure from sequence and several novel technologies that we have recently developed in our laboratory. Our current focus is on leveraging these technological advances to identify patient-specific therapies targeting orphan diseases that have no known cure or more common disorders to which there is a poor prognosis, such as drug resistant cancers.

Scripps Research

A leading nonprofit biomedical research institute, Scripps Research is ranked No. 1 in the world by Nature Index for scientific innovation. *U.S. News & World Report* consistently ranks our graduate school in the top 10 in the United States. Our unique structure merges foundational studies in biology, chemistry and computer science with translational research to produce the next generation of drugs and advances in digital and precision medicine.

On campuses in California and Florida, scientists in the institute's five academic research departments work hand-in-hand with researchers of the Scripps Research Translational Institute and Calibr, our drug discovery division. We train the next generation of scientific leaders, expand the frontiers of human knowledge and accelerate the development of new medicines to improve lives around the planet. Charity Navigator has given Scripps Research four stars, its highest rating.

To learn more about Scripps Research, please visit scripps.edu. To register for or learn more about events on the Florida campus, please call (561) 228-2015 or visit **scripps.edu/events**.

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Expansion Therapeutics

Founded in November 2016, Expansion Therapeutics, Inc. is a private company focused on the discovery and development of ribonucleic acid (RNA) targeted small molecule medicines. Ribonucleic acid (RNA) is a polymeric molecule essential in various biological roles in coding, decoding, regulation, and expression of genes. Expansion is focused on expansion repeat disorders, which are responsible for over 30 neurological and neuromuscular diseases, and for which there are currently no satisfactory therapies. Our initial disease focus, myotonic dystrophy type 1 (DM1), is the most frequent cause of adult onset muscular dystrophy. Expansion Therapeutics' proprietary technology is based on pioneering work from the lab of Dr. Matthew D. Disney of the Florida campus of Scripps Research. In January 2018, they closed $55.3 million in Series A financing, co-led by 5AM Ventures, Kleiner Perkins, Novartis Venture Fund, and Sanofi Ventures with participation from RA Capital Management and Alexandria Venture Investments. The financing will allow Expansion to advance our portfolio of novel RNA-targeted small molecule medicines to treat rare diseases. With facilities in San Diego, California and Jupiter, Florida, Expansion Therapeutics currently employs 20 individuals in the U.S. It also has a seven-member board of directors, and six-member scientific advisory board comprised of leaders in the field of RNA-targeted small molecule chemistry and biology, RNA folding and structural biology. Additional information about the company and job openings are available at **www.expansionrx.com**.

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