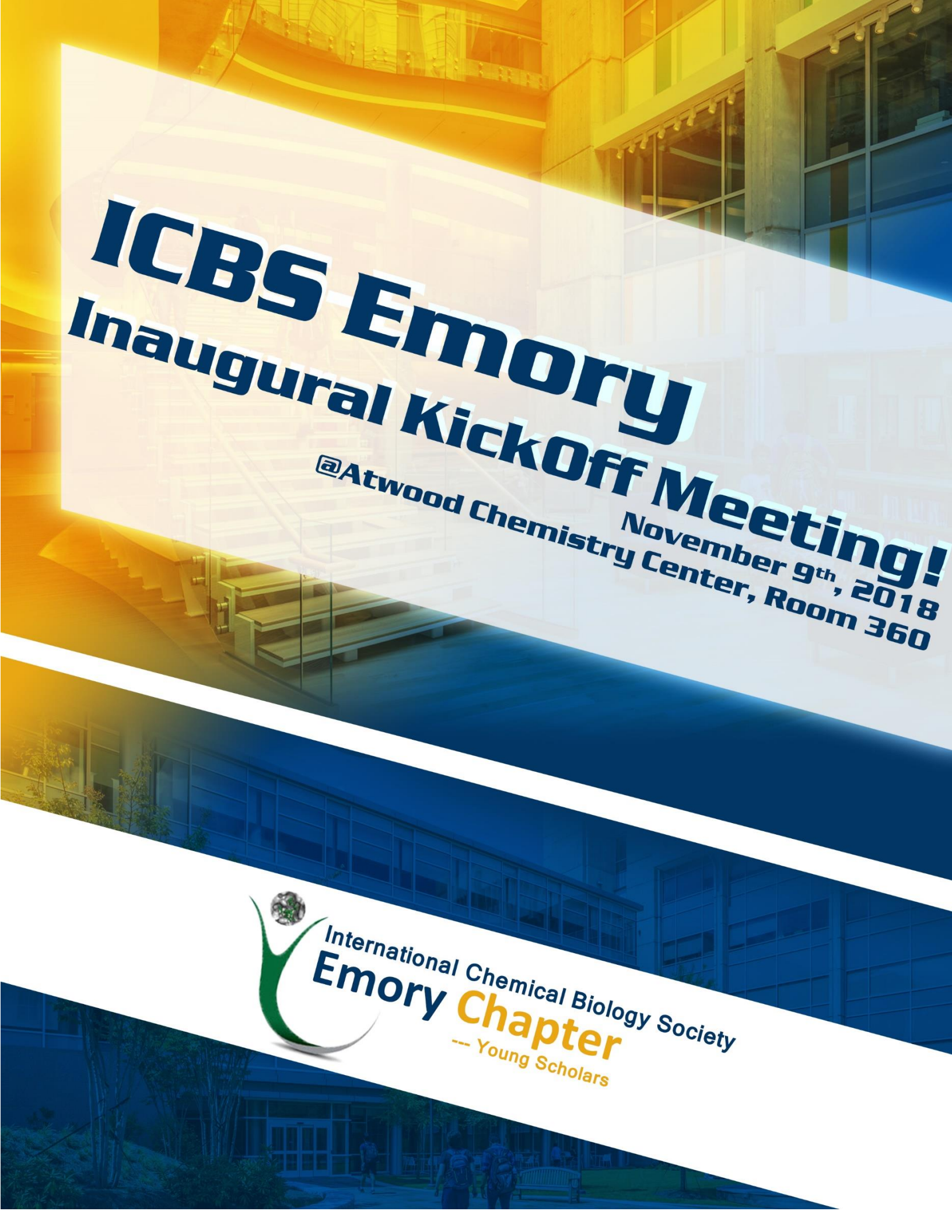
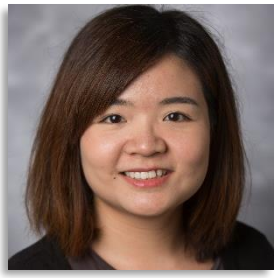

ICBS Emory
Inaugural KickOff Meeting!
@Atwood Chemistry Center, Room 360
November 9th, 2018
International Chemical Biology Society
Emory Chapter
--- Young Scholars

Organizing Committee



Kun Qian, PhD
President
Postdoctoral Fellow (Haian Fu Group)

Sean Doyle
Vice-President
MD/PhD Student (Haian Fu Group)

Taylor P. A. Hari, PhD
Vice-President
Postdoctoral Fellow (Bill Wuest Group)

Aimee Sanford
Event Coordinator
PhD Student (Jen Heemstra Group)

Amber Scharnow
Treasurer
PhD Student (Bill Wuest Group)

Xuan (Novak) Yang
Secretary
Masters Student (Haian Fu Group)

Our Mission

The Emory Chapter of the ICBS is a student and postdoctoral organization affiliated with the International Chemical Biology Society. We were founded in the summer months of 2018 and represent an independent, non-profit organization dedicated to promoting research and educational opportunities at the interface of chemistry and biology. We aim to provide a cross-disciplinary forum that unites young researchers across the entire Emory network, with academic, non-profit organizations, government, and industry experts in the Greater Atlanta and southeast area. This forum will facilitate communication of new research, improve collaborative endeavors, and help translate the power of chemical biology to advancing human health.

ICBS Emory: Inaugural Research Symposium

09:00 – 09:30 ICBS Registration, Refreshments, Meet & Greet

09:30 – 09:40 Welcome and Introductory Remarks by Kun Qian, President

SESSION I – Atwood Hall (Rm 360)
Discussion Leader: Sean Doyle

Valentina González-Pecchi (*Department of Pharmacology, Fu Group*)

09:40 – 10:00 Targeting Oncogenic NSD3-Mediated Protein-Protein Interactions

Nusaiba Baker (*Emory School of Medicine, Salaita Group*)

10:00 – 10:20 Elucidation of DNA Enzyme Nanoparticles in Regulating Gene Expression in Inflammation

Justin A. Shapiro, PhD (Department of Chemistry, Wuest Group)

10:20 – 10:40 Chemical Synthesis of Iron-Binding Natural Products with Diverse Bioactivity from Marine Microbiomes

10:40 – 11:00 Coffee Break

SESSION II – Atwood Hall (Rm 360)
Discussion Leader: Amber Scharnow

Prof. Neha Garg (*Georgia Institute of Technology*)

11:00 – 11:30 Invited Young Investigator Career Talk

Power Hour (Panel Discussion)

11:30 – 12:30 *A Discussion of Topics Relating to Academic Careers and the Field of Chemical Biology*

Prof. Neha Garg (*Georgia Institute of Technology*)
Prof. Haian Fu (*Dept. of Pharmacology*)
Prof. Jen Heemstra (*Dept. of Chemistry*)
Prof. Bill Wuest (*Dept. of Chemistry*)
Prof. Ben Shen (*The Scripps Research Institute, FL*)
Prof. Randy Hall (*Dept. of Pharmacology*)
Prof. Cassandra Quave (*Dept. of Dermatology*)

12:30 – 1:15 Lunch Break

SESSION III – Atwood Hall (Rm 360)
Discussion Leader: Aimee Sanford

Ashley R. Cross (*Department Pediatrics, Goldberg Group*)

1:20 – 1:40 Remodeling of O Antigen Chain-Length in Mucoid *Pseudomonas aeruginosa*

Tewoderos Ayele (*Department of Chemistry, Heemstra Group*)

1:40 – 2:00 Fluorescent Labeling of mRNA using Self-Alkylating Ribozymes

Suzanne G. Mays (*Department of Biochemistry, Ortlund Group*)

2:00 – 2:20 Discovery of the First Low Nanomolar LRH-1 Agonist Through Structure-Guided Design

2:20 – 2:30 Coffee Break

SESSION IV – Atwood Hall (Rm 360)
Discussion Leader: Taylor P. A. Hari

Prof. Ben Shen (*The Scripps Research Institute, FL*)

2:30 – 3:30 Microbial Genomics: New Opportunities for Natural Product Biosynthesis, Engineering, and Drug Discovery

3:30 – 3:40 Closing Remarks

Presentation Abstracts

TARGETING ONCOGENIC NSD3-MEDIATED PROTEIN-PROTEIN INTERACTIONS

Valentina González-Pecchi[1,*], Jinglin Xiong[1], Andrew Ivanov[1,2], Yuhong Du[1,2], and Haian Fu[1,2]

[1]*Department of Pharmacology, Emory University, Atlanta, GA.*
[2]*Emory Chemical Biology Discovery Center, Emory School of Medicine, Atlanta, GA.*
[*]*Fulbright Scholar, Chile*

Epigenetic regulation has emerged as a promising field for the development of cancer therapeutics. NSD histone lysine methyltransferases (HMT) have been shown to play critical roles in cancer. A splice variant of NSD3, termed NSD3S, is found as chimeric oncogenic fusion protein in NUT midline carcinoma, NSD3-NUT. In further support of its role in cancer, NSD3S is also amplified in multiple solid tumors and shown to promote oncogenic programs in leukemia. Thus, understanding how NSD3S, a NSD3 protein without its catalytic domain, transmits cell growth signals may lead to novel therapeutic strategies. Here we report the discovery and characterization of a NSD3S-mediated signal complex. Through a high-throughput PPI detection technology, we identified a novel NSD3S partner, a transcription factor, MYC. MYC is one of the most commonly amplified oncogenes across tumor types and is essential for different cancers. Using multiple binding assays, we demonstrated that NSD3S interacts with MYC and enhances MYC protein stability and transcriptional activity. Interestingly, NSD3S is known to interact with BRD4, a bromodomain protein that has been functionally linked to MYC. Our discovery of the NSD3S-MYC interaction suggests a novel BRD4 regulatory mechanism and a potential target for perturbing the NSD3-mediated oncogenic pathway. Small molecule inhibitors of NSD3S-MYC and NSD3S-BRD4 interaction will be a valuable tool for understanding the function of NSD3S on cancer and for therapeutic discovery. To achieve this goal, we designed and developed a time-resolved fluorescence resonance energy transfer (TR-FRET) assay to monitor the interaction of NSD3S-MYC and NSD3S-BRD4. The assays were further miniaturized into a 1536-well ultra-high-throughput screening (uHTS) format with robust performance. Compounds screening has led to the identification of promising hits for further chemical optimization. Our study suggests a novel regulatory axis mediated by BRD4-NSD3S-MYC and a novel therapeutic approach for treating patients with NSD3S driven tumors.

ELUCIDATION OF DNA ENZYME NANOPARTICLES IN REGULATING GENE EXPRESSION IN INFLAMMATION

Nusaiba Baker[1,2], and Khalid Salaita[3]

[1]*Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA.*
[2]*Emory School of Medicine, Emory University, Atlanta, GA.*
[3]*Department of Chemistry, Emory University, Atlanta, GA.*

Inflammation is an augmented response to potentially dangerous agents in our body. Augmented immune responses can occur in the case of asthma, an overwhelming inflammatory disorder characterized by airway hyperresponsiveness and difficulty breathing. In autoimmune diseases, such as inflammatory bowel disease or rheumatoid arthritis, the immune system mistakenly identifies its own "self" as foreign. In either case, this inflammation can result in decreased quality of life and societal and economic burden. A main cause of inflammatory symptoms is the release of cytokines from immune cells. These cytokines, such as IL-4, IL-5, TNF-a, and IFN-g signal to the body to cause symptoms such as fever, fatigue, swelling, and cachexia. GATA3, a transcriptional activator, is involved in T lymphocyte

differentiation and signaling, particularly in the Th2 subtype, and regulates the expression of cytokines such as IL-4, IL-5, and IL-13. Accordingly, knock down of GATA3 and subsequent cytokine expression is a promising strategy for treatment of inflammatory disease. A range of antisense and RNAi technologies have been tested, and among these approaches, DNA enzymes (Dzs) have shown the greatest promise in animal models and Phase 1 clinical trials.

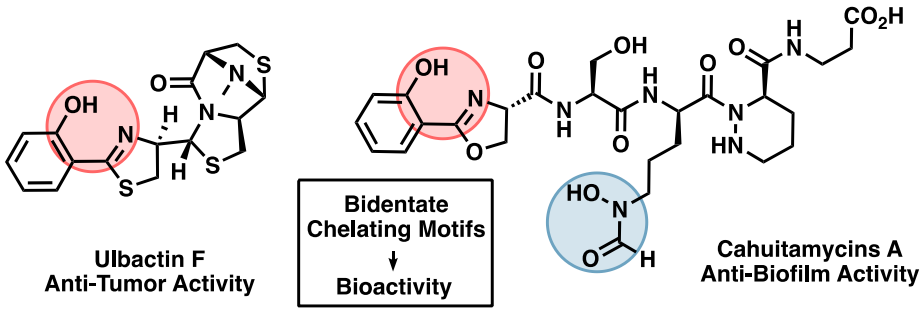
Dzs are canonical DNA oligonucleotides that catalytically degrade a specific complementary RNA sequence. Despite the success of soluble Dzs as a therapeutic intervention, delivering highly charged oligonucleotides across the plasma membrane, and preventing nuclease degradation are major challenges. To address these problems, we have developed GATA3 DNAzyme nanoparticle conjugates that elucidate the stability and delivery issues in the lung. Preliminary evidence shows that conjugating ~100 Dzs to a 14-nm gold particle forms a complex (DzNP) that improves airway function in mouse models of asthma. Importantly, DzNPs use one order of magnitude lower Dz dose compared to their soluble counterparts. Thus, we have established a novel method of gene regulation using a synthetic biomaterial. Further, we have identified different mechanisms by which this technology can be delivered. This research will provide a foundation for future development of nanoparticle-based therapeutic strategies for numerous diseases.

CHEMICAL SYNTHESIS OF IRON-BINDING NATURAL PRODUCTS WITH DIVERSE BIOACTIVITY FROM MARINE MICROBIOMES

Justin A. Shapiro, and William M. Wuest

Department of Chemistry, Emory University, Atlanta, GA.

Marine microbiomes are an under-explored repository of diverse natural products due to fluctional chemical composition, irregular nutrient availability, and complex symbiotic networks of organisms. In order to gain competitive advantage, many microbes excrete molecules containing high-affinity bidentate chelating ligands to scavenge micronutrient metals. The bioactive properties of these scaffolds and their potential as antibiotics is becoming more widely appreciated. Our lab is currently engaged in the total synthesis and biological/physicochemical evaluation of two such molecules, the tumor-inhibiting ulbactin F and the biofilm-inhibiting cahuitamycin A.



REMODELING OF O ANTIGEN CHAIN-LENGTH IN MUCOID *PSEUDOMONAS AERUGINOSA*

Ashley R. Cross[1,2,3], Joanna B. Goldberg[2,3]

[1]*Emory Laney Graduate School, Microbiology and Molecular Genetics Program, Atlanta, GA*
[2]*Department of Pediatrics, Division of Pulmonary, Allergy & Immunology, Cystic Fibrosis, and Sleep, Children's Healthcare of Atlanta, Atlanta, GA*
[3]*Emory+Children's Center for Cystic Fibrosis and Airway Disease Research, Emory University School of Medicine, Atlanta, GA*

Regulation of lipopolysaccharide (LPS) O antigen chain-length in gram-negative bacteria is important for attachment, virulence, and survival within a host. In the lungs of people with cystic fibrosis (CF) *Pseudomonas aeruginosa* chronic isolates emerge that do not express O antigen, resulting in an LPS-rough phenotype. In addition, these chronic isolates switch from a nonmucoid to a mucoid phenotype characterized by the overproduction of the exopolysaccharide alginate. Therefore, it appears that O antigen expression and the mucoid phenotype are inversely regulated. *P. aeruignosa* expresses two O antigen chain-length regulators, Wzz1 and Wzz2, that are required to assemble two preferred O antigen modalities, termed long and very long, respectively. How Wzz proteins regulate O antigen chain-length in gram-negative bacteria is not known. Likewise, how Wzz proteins themselves are regulated remains unclear. To begin to define the regulatory network controlling O antigen chain-length in *P. aeruginosa*, we built on the observation that rare O antigen expressing mucoid strains have altered O antigen modalities. We show that mucoid laboratory strain PDO300 (derived from the nonmucoid strain PAO1) and mucoid CF isolates produce less Wzz2 compared to nonmucoid strains and that this regulation is dependent on AlgT, an alternative sigma factor with a large regulon that includes genes of the alginate biosynthesis operon. We further determined that regulation of Wzz2 is at the level of transcription initiation and confirm AmrZ, a transcription factor highly expressed in mucoid strains, to be a repressor of wzz2 promoter activity. These experiments identify the first transcriptional regulator of O antigen chain-length in *P. aeruginosa* and support a model in which the transition to a chronic mucoid infection is accompanied by down regulation of very long O antigen prior to the establishment of an LPS-rough phenotype.

FLUORESCENT LABELING OF mRNA USING SELF-ALKYLATING RIBOZYMES

Tewoderos Ayele, Satheesh Ellipilli, Steve Knutson, and Jen Heemstra

Department of Chemistry, Emory University, Atlanta, GA.

Intracellular transport of transcribed mRNA causes asymmetric distribution of protein and plays an essential role in cell development and physiology. To understand the mechanism of mRNA localization, there have been several efforts to fluorescently label RNA in live cells. Such techniques include fluorescence in-situ hybridization, molecular beacons, aptamer-fluorescent/fluorogenic molecule pair, and attachment of sequence recognizing fluorescent proteins. Even though these techniques have advanced the field of RNA imaging, they suffer from limitations such as requirement of cell fixation, attachment of large molecules that could perturb native RNA localization, or rely on non-covalent interactions. Herein, it is proposed to develop a covalent RNA labeling technique in a live-cell model that avoids the inherent limitations exhibited in the previously used systems. To achieve this task, we are developing a fluorescently self-alkylating ribozyme that can be attached to a mRNA of interest. This technique will allow for the dynamic visualization of target mRNA using fluorescent microscopy.

DISCOVERY OF THE FIRST LOW NANOMOLAR LRH-1 AGONIST THROUGH STRUCTURE-GUIDED DESIGN

Suzanne G. Mays[1], Autumn R. Flynn[2], Jeffrey L. Cornelison[2], C. Denise Okafor[1], Heather N. Donaldson[1], Michael Dugan[2], Elizabeth J. Millings[1,3], Rohini Polavarapu[3], John W. Calvert[3], Nathan Jui[2], and Eric A. Ortlund[1]

Departments of [1]Biochemistry, [2]Chemistry, and [3]Surgery, Emory University, Atlanta, GA.

As a key regulator of metabolism and inflammation, the orphan nuclear hormone receptor, Liver Receptor Homolog-1 (LRH-1), has potential as a therapeutic target for obesity-associated metabolic diseases. Discovery of LRH-1 modulators has been difficult, in part due to the tendency for synthetic compounds to bind unpredictably within the lipophilic binding pocket. Using an iterative, structure-guided approach, we exploit a newly-discovered polar interaction to lock agonists in a consistent orientation. This enabled the discovery of the first low nanomolar LRH-1 agonist, one hundred times more potent than the previous best modulator. We demonstrate that the new agonist is active *in vivo* and elucidate a novel mechanism of action, which relies upon specific polar interactions deep in the LRH-1 binding pocket. These studies constitute major progress in developing LRH-1 modulators with potential clinical utility.

MICROBIAL GENOMICS: NEW OPPORTUNITIES FOR NATURAL PRODUCT BIOSYNTHESIS, ENGINEERING, AND DRUG DISCOVERY

Prof. Ben Shen

The Scripps Research Institute, Florida

Natural products are among the best sources of drugs and drug leads and serve as outstanding small molecule probes for dissecting fundamental biological processes. Natural product biosynthesis continues to push the frontier of modern chemistry, biochemistry, and molecular biology by revealing novel chemical reactions, complex enzyme systems, and intricate regulatory mechanisms. The progress made in the last two decades in connecting natural products to the genes that encode their biosynthesis has fundamentally changed the landscape of natural products research and sparked the emergence of a suite of contemporary approaches to natural products discovery. Synthetic biology has made it possible to produce designer natural products by rational metabolic pathway engineering. Genome mining has allowed targeted discovery natural product scaffolds by exploring the vast biosynthesis repertoire found in Nature. Selected examples from our current studies will be presented to showcase the impact of microbial genomics on natural product discovery and inspiration from natural product biosynthesis for novel chemistry, enzymology, and drug discovery.