BIOGRAPHICAL SKETCH

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NAME: Hagler, Lauren

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POSITION TITLE: Postdoctoral Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Agnes Scott College		08/2010	12/2011	Chemistry
The University of Alabama	BS	01/2012	05/2015	Chemistry/ Biochemistry
University of Illinois at Urbana-Champaign	PhD	08/2015	05/2020	Chemistry
Stanford University	Postdoctoral Fellow	07/2020	Present	Biochemistry

A. Personal Statement

My long-term research interests involve understanding the complex dynamics of RNA structure formation in cells and designing small molecule drugs to target RNAs implicated in disease. To support these interests, I have pursued academic training and research experiences to build a foundation for a future as an academician at the interface of biochemistry, chemical biology and organic chemistry. As an undergraduate at the University of Alabama in Prof. Silas Blackstock's research group, I built an appreciation for fundamental physical organic chemistry and synthetic techniques in small molecule co-crystallization. During a summer rotation in the Zimmerman group at the University of Illinois at Urbana-Champaign (UIUC), I read a letter from a little girl named Kate who suffered from myotonic dystrophy type 1 (DM1) and was thanking the group for their research efforts to find a cure for the disease that would allow her to play on the playground with her friends. That interaction and the group's sustained relationship with local patient families through the Muscular Dystrophy Association drew a connection between what I was studying in the lab and the people I was hoping to help. Thus, my view of scientific research shifted from a personal interest to a passionate endeavor to contribute to my community and move drug discovery and personalized medicine into a new frontier. I subsequently joined the Zimmerman group after that rotation to study and design drugs for the treatment of DM1. My dissertation research focused on understanding the relationship between the function of small molecule drugs and the structure of their nucleic acid targets, with a specific interest in the trinucleotide repeat RNA and DNA that causes DM1. I developed a simple computational protocol to study the conformation dynamics of uracil base-flipping in trinucleotide repeat RNA (*Can. J. Chem. 2020*) and designed new molecules through structure-based drug design that harness base-binding as means of selectivity (*Bioorg. Med. Chem. Lett. 2019*; *J. Am. Chem. Soc. 2020*). The principles studied computationally were tested experimentally, using the RNA and DNA structure in combination with in situ click chemistry to identify new sequence-selective transcription inhibitors for DM1 (*Biochemistry 2020*).

I am currently a Stanford Propel Postdoctoral Scholar in the Department of Biochemistry studying how RNA interacts with proteins and other RNAs in the cells using quantitative and high-throughput genomic measurements. Overall, my diverse research interests at the interface of fundamental biochemistry and translational chemical biology provide a unique opportunity for my future research program to advance personalized medicine from the position of RNA to have a predictive understanding of RNA-mediated processes and the impact of RNA-targeting drugs.

1. **Hagler, L.D.;** Krueger, S.B.; Luu, L.M.; Mitchell, N.L.; Vergara, J.I. Curet, L.D.; Zimmerman, S.C. A Versatile Target-Guided Screen for Discovering Multivalent, Bidirectional Transcription Inhibitors of Trinucleotide Repeat Diseases. *ACS Med. Chem. Lett.* ***2021****, 12, 935-940.*
2. **Hagler, L.D.***; Luu, L.M.*; Tonelli, M.; Lee, J.; Hayes, S.; Krueger, S.B.; Vergara, J. I.; Butcher, S.E.; Zimmerman, S.C. Expanded DNA and RNA Trinucleotide Repeats in Myotonic Dystrophy Type 1 Select Their Own Multitarget, Sequence-Selective Inhibitors. *Biochemistry* **2020**, *59*, 3463-3472. *Indicates shared co-first authorship.
3. Sadée, C.*; **Hagler, L.D.***; Becker, W.R.; Jarmoskaite, I.; Vaidyanathan, P.P.; Denny, S.K.; Greenleaf, W.J.; Herschlag, D. A comprehensive thermodynamic model for RNA binding by the Saccharomyces cerevisiae Pumilio protein PUF4. Under Review. Nature Portfolio preprint. *Indicates shared co-first authorship.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020 – Present	Postdoctoral Fellow, Stanford University
2016 – 2018	Chemistry-Biology Interface (CBI) Training Program Fellow, National Institutes of Health
2015 – Present	Member, National Organization for the Professional Advancement of Black Chemists and Chemical Engineers (NOBCChE)
2015 – Present	Member, Women Chemists Committee
2015 – 2020	Graduate Research Assistant, University of Illinois at Urbana-Champaign
2014 – Present	Member, American Chemical Society
2013 – 2015	Undergraduate Research Assistant, University of Alabama

Honors

2019	Women in Chemistry (WiC) Inclusive Leadership Award, University of Illinois
2017	Ford Foundation Fellowship Program (Honorable Mention)
2014 – 2015	ACS Scholar, American Chemical Society

C. Contributions to Science

1. **Physical Organic Principles Electron Donor-Acceptor Co-crystallization** Beginning in the fall of 2013, I worked under Dr. Silas Blackstock at the University of Alabama to better understand the relationship and interactions of electron donors and electron acceptors through co-crystallization. The target donor of my research was the electron-rich pyrazole donor 3,5-di(p-anisyl)-4H-pyrazole (DA-4HP). The synthesis of the target molecule gave me valuable experience with synthetic techniques and research in general.
    a. **Hagler, L.D.;** Kelley, M. and Blackstock, S. C. (2014). *Increasing the Pi Electron Density in a Pyrazole Donor Molecule to Optimize its Donor-Acceptor Bonding with Quinones.* Poster Presented at the annual Undergraduate Research Conference at The University of Alabama, Tuscaloosa, AL.
2. **Structure-Based Design of DM1 Therapeutics.** The trinucleotide repeat expansion diseases (TREDs), make up a class of as many as 41 rare and incurable illnesses, including ALS, fragile X syndrome, myotonic dystrophy (DM1 and DM2), and Huntington's disease. The trinucleotide repeats DNA that causes DM1, $d(CTG•CAG)^{exp}$, can slip out of the double strand duplex to form stable secondary structures. Upon transcription, $r(CUG)^{exp}$ forms A-form double helix hairpins with mismatched U bases and sequesters MBNL1 and other proteins into the nucleus causing many of the symptoms of the disease. I have developed a simple computational protocol to understand the binding of small molecule ligands to $r(CUG)^{exp}$ and $d(CTG)^{exp}$ hairpins in a base flipping mode, harnessing base-binding interactions to yield sequence-selective inhibitors. These studies resulted in the discovery of novel macrocyclic intercalators that bind to d(CTG) repeats selectively and act as transcription inhibitors. Further, we have utilized this protocol to optimize and enhance the binding properties of our suite of nucleic acid targeting small molecules and oligomers.

a. **Hagler, L.D.;** Bonson, S.E.; Kocheril, P.A.; Zimmerman, S.C. Assessing the Feasibility of U-base Flipping in RNA-small Molecule Complexes Using Molecular Dynamics Simulations. *Can. J. Chem.* **2020**, *98*, 261-269.
b. Serrano, J.F.; Lee, J.; Curet, L.D.; **Hagler, L.D;** Bonson, S.E.; Schuster, E.J; Zimmerman, S.C. Development of Novel Macrocyclic Small Molecules that Target CTG Trinucleotide Repeats. *Bioorg. Med. Chem.* **2019**, *27*, 2978-2984.
c. Chien, C.; Wu, P.; Stange, R.; Chang, C.; Lai, Z.; **Hagler, L.D.;** Zimmerman, S.C.; Hou, M. Structural Basis for Targeting T:T Mismatch With Triaminotraizine-acridine Conjugate Induces a U-shaped Head to Head Four-Way Junction in CTG Repeat DNA. *J. Am. Chem. Soc.* **2020**, *142,* 11165-11172.

3. **Discovery of Multitarget, Multivalent Inhibitors of DM1.** The DNA and RNA responsible for TREDs are unique in their structure compared to other protein or nucleic acid drug targets. The repeated nature of the structures they form make them highly amenable to multivalent targeting, thereby increasing drug selectivity and affinity. A common theme has emerged in our recent findings: multivalent binding is needed to provide a more effective ligand. Thus, we developed a method for the rapid detection of selective, multivalent inhibitors from smaller ligand fragments with the hope that some of these might also serve as multitarget agents. We developed a novel library approach that uses the template-assisted, azide-alkyne click reaction in a selection format with both $d(CTG)_{16}$ and $r(CUG)_{16}$ targets. Hit dimeric compounds were able to bind tighter than their monomeric counterparts to d(CTG) and r(CUG) repeats, form specific interactions with UU mismatches in RNA hairpin structures in solution, and inhibit transcription and r(CUG)-MBNL interactions *in vitro*. A parallel, target-guided screen with d(CTG) hairpins resulted in even more small molecules able to undergo an *in situ* click reaction selectively on the target, including some novel ligands for DM1. Many products were able to stall the formation of $r(CUG)_{90}$ and $r(CAG)_{90}$ at low micromolar concentrations.
   a. **Hagler, L.D.*;** Luu, L.M.*; Tonelli, M.; Lee, J.; Hayes, S.; Bonson, S.E.; Vergara, J. I.; Butcher, S.E.; Zimmerman, S.C. Expanded DNA and RNA Trinucleotide Repeats in Myotonic Dystrophy Type 1 Select Their Own Multitarget, Sequence-Selective Inhibitors. *Biochemistry* **2020**, *59*, 3463-3472. *Indicates shared co-first authorship.
   b. **Hagler, L.D.;** Luu, L.M.; Zimmerman, S.C. Template-Assisted Click Chemistry as a Therapeutic Strategy for Myotonic Dystrophy Type 1 (DM1). 258th ACS National Meeting & Exposition, San Diego, CA, August 2019.
   c. **Hagler, L.D.;** Krueger, S.B.; Luu, L.M.; Lanzendorf, A.N.; Mitchell, N.L.; Vergara, J.I. Curet, L.D.; Zimmerman, S.C. A Versatile Target-Guided Screen for Discovering Multivalent, Bidirectional Transcription Inhibitors of a Trinucleotide Repeat Disease. *ACS Med. Chem. Lett.* **2021***, 12,* 935-940.

4. **Development of Quantitative Methods to Measure and Predict RNA Interactions in Cells.** The genomic revolution spurred a new phase of discovery, including the identification of many regulatory roles of RNA. These studies have given us a map of RNA regulatory connections and, but this map makes only basic predictions of overarching processes and does not allow us to navigate from one cellular state to another. My goal is to bring us to the next level of understanding, focusing on RNA to (1) build quantitative physical models for its behavior and interactions in cells and (2) how these properties lead to downstream effects in gene regulation and expression. In developing "Quantitative Cellular Biochemistry" (QCB) as an experimental framework, I will integrate biochemistry, biophysics, and genomics to strategically make hundreds of thousands of quantitative biochemical measurements in cells, employing designed mRNA libraries that systematically vary factors responsible for RNA-protein interactions, RNA folding, and, more deeply, the cellular factors that affect these interactions.
   a. Sadée, C.*; **Hagler, L.D.*;** Becker, W.R.; Jarmoskaite, I.; Vaidyanathan, P.P.; Denny, S.K.; Greenleaf, W.J.; Herschlag, D. A comprehensive thermodynamic model for RNA binding by the Saccharomyces cerevisiae Pumilio protein PUF4. Under Review. Nature Portfolio preprint. (*Authors contributed equally)

Complete List of Published Work in My Bibliography:
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