BIOGRAPHICAL SKETCH

NAME: **Lauren D. Hagler**

eRA COMMONS USER NAME: LAUREN_HAGLER

POSITION TITLE: Post-doctoral Scholar

EDUCATION/TRAINING

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
University of Alabama	BS	01/2012	05/2015	Chemistry (Biochemistry)
University of Illinois at Urbana-Champaign	PHD	08/2015	05/2020	Chemistry (Organic)

A. Personal Statement

My long-term research and career 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 in 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. For my graduate training at the University of Illinois at Urbana-Champaign, I moved toward small molecule drug discovery in the fields of organic chemistry, chemical biology, and computational chemistry under the advisement of Prof. Steven C. Zimmerman. 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 myotonic dystrophy type 1 (DM1). I developed a simple computational protocol to study the conformation dynamics of uracil base-flipping in trinucleotide repeat RNA and developed new molecules through structure-based drug design that harness base-binding as means of selectivity. The principles studied computationally were tested experimentally, using RNA and DNA structure and in situ click chemistry to identify new sequence-selective transcription inhibitors for DM1. Upon completion of my doctorate training, I sought a post-doctoral advisor and research group that would expand my expertise in RNA biology to support my research goals in my future academic career at a top research institution. I am particularly interested in developing predictive models for RNA structure and folding in cells that can be ultimately applied to a mechanistic understanding of alternative splicing. Prof. Herschlag is an internationally recognized leader in the fields of enzyme catalysis, RNA folding, and RNA-protein interactions. His diverse interests allow him to mentor a broad range of well-rounded predoctoral and postdoctoral trainees. His commitment to and passion for training the next generation is also an inspiration for which I hope to learn from. The proposed training plan will not only allow me to develop conceptual and technical training through the research aims but also non-technical skills and professional development through workshops and career development opportunities. From the experiences I have gained and will continue, I hope to serve as a mentor to other African American women by acting as a role model, leader, and mentor. Overall, I feel that my choice of sponsor, institution, and research interests serve an overall purpose of helping a diverse group of people, inside and outside of a laboratory setting, as academic researcher and educator.

B. Positions and Honors

Positions and Employment

2013-2015 Undergraduate Research Assistant, University of Alabama
2014 Student Assistant (General Chemistry, Office of Disability Services), University of Alabama
2014 Undergraduate Teaching Assistant (Organic Chemistry Lab), University of Alabama
2015-2016 Graduate Teaching Assistant (Organic Chemistry I), University of Illinois at Urbana-Champaign
2015-2020 Graduate Student Research Fellow, University of Illinois at Urbana-Champaign
2017 Graduate Teaching Assistant (Organic Chemistry I), University of Illinois at Urbana-Champaign
2020- Post-doctoral Scholar, Stanford University

Other Experience and Professional Membership

2012 Tau Sigma National Honor Society
2012 Golden Key International Honor Society
2013 Delta Epsilon Iota Academic Honor Society
2014 Gamma Sigma Epsilon Chemistry Honor Society
2014 American Chemical Society
2015 Women Chemists Committee
2015 National Organization for the Professional Advancement of Black Chemists and Chemical Engineers (NOBCChE)
2015 Associate Fellow, Summer Pre-Doctoral Institute, University of Illinois at Urbana-Champaign
2016-2017 Student Committee Member, Senate Admissions Committee, University of Illinois at Urbana-Champaign
2016-2019 Peer Mentor, Sloan University Center for Exemplary Mentoring, University of Illinois at Urbana-Champaign
2017-2018 Assistant Director for Graduate Diversity and Program Climate Search Committee, UIUC Department of Chemistry
2018 Retreat for Graduate Women Planning Committee, UIUC Department of Chemistry
2018-2019 Sylvia M. Stoesser Lecture Planning Committee, UIUC Department of Chemistry
2018-2019 Diversity Committee Student Representative, UIUC Department of Chemistry
2018-2019 Graduate Student Liaison, University of Illinois Student Chapter of NOBCChE
2019-2020 Chapter President, University of Illinois Student Chapter of NOBCChE

Honors

2014-2015 ACS Scholar, American Chemical Society
2015-2016 Roger Adams Fellow, University of Illinois at Urbana-Champaign
2015-2016 Sloan Scholar, Alfred P. Sloan Foundation's Minority Ph.D. (MPHD) Program
2016-2017 R. C. Fuson Fellow, University of Illinois at Urbana-Champaign
2016-2018 Chemistry-Biology Interface (CBI) Training Program Fellow, National Institutes of Health
2017 Ford Foundation Fellowship Program (Honorable Mention)
2017-2018 University of Illinois Snyder Fellow, University of Illinois at Urbana-Champaign
2018-2019 Sloan Research Prize Fellow, University of Illinois at Urbana-Champaign
2018-2019 Novartis Fellow, University of Illinois at Urbana-Champaign
2018-2019 University of Illinois Organic Area Pines Travel Award
2019 University of Illinois Organic Area Fuson Travel Award
2019 Women in Chemistry (WiC) Inclusive Leadership Award, University of Illinois

C. Contributions to Science

1. **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.

2. **Development 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. Lee, J.; Bai, Y.; Chembazhi, U.V.; Peng, S.; Yum, K.; Luu, L.M.; Hagler, L.D.; Serrano, J.F.; Chan, H.Y.E.; Kalsotra, A.; Zimmerman, S.C. Intrinsically Cell-penetrating Multivalent and Multitargeting Ligands for Myotonic Dystrophy Type 1. *Proc. Natl. Acad. Sci.* **2019**, *116*, 8709-8714.
b. 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.
c. 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.
d. Hagler, L.D.; Luu, L.M.; Bonson, S.E.; 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. *Manuscript Submitted.*