BIOGRAPHICAL SKETCH

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NAME: Carrigan-Broda, Theodore

eRA COMMONS USER NAME (credential, e.g., agency login): THEODOREBRODA

POSITION TITLE: MD/PhD Candidate

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
College of Charleston, Charleston, South Carolina	BS	07/2014	07/2017	Chemistry & Biochemistry
UMass Chan Medical School, Worcester, MA	MD/PHD	07/2019	06/2027 (tentative)	Clinical Medicine & Biomedical Science

A. Personal Statement

I am an inquisitive, results-oriented translational therapeutics scientist; I integrate medicinal chemistry, pharmacology, and comparative medicine to develop innovative molecular modalities for diverse, impactful clinical applications. Currently, I am an MD/PhD candidate conducting thesis research in Dr. Anastasia Khvorova's lab in the RNA Therapeutics Institute (RTI) at UMass Chan Medical School; my focus is design, synthesis, and characterization of modified siRNA architecture for optimized metabolic stability, potency, accumulation, and duration of effect in extrahepatic tissues. I am concurrently training in clinical medicine to better understand the concerns of patients and providers; ultimately, I will apply my physician-scientist training to address unresolved clinical needs by expanding the armamentarium of RNA therapeutics.

I began my scientific career with a bachelor's degree in biochemistry and chemistry (*summa cum laude*) at the College of Charleston, including synthetic chemistry research under Frederick Heldrich and a thesis characterizing novel organosilicon compounds under Gamil Guirgis. These experiences provided me with broadly applicable technical skills in chemical synthesis, spectroscopy, molecular modeling, experimental design, and scientific communication. Specifically, my studies of molecular modeling introduced me to pharmacophore modeling, which piqued my interest in medicinal chemistry as a practical application of my burgeoning scientific acumen.

Although I appreciated basic science training, I sought an applied research opportunity with practical objectives. Consequently, I worked in the drug discovery lab of Mark Hamann at the Medical University of South Carolina, wherein I investigated novel semisynthetic derivatives of manzamine A for potential antimalarial and antineoplastic activity. I enjoyed this opportunity to investigate potential solutions to clinical problems using my ingenuity and knowledge of molecular science, motivating my current training in therapeutics research. I also trained as an Emergency Medical Technician to acquire clinical knowledge and patient interaction, which inspired me to align my research interests with my humanistic values and newfound clinical interests.

I subsequently elected to pursue a Medical Scientist Training Program at UMass Chan Medical School to actualize my career objective of empowering clinical medicine with strategic therapeutic development. I have completed my preclinical medical education, USMLE Step 1 board exam, medicine and neurology clerkships, and graduate school qualifying exam. Following my MSTP training, I intend to continue my professional development in a Physician-Scientist Training Program and establish my research niche in academic medicine or the pharmaceutical industry.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2024 - Neonate Cuddler, Cuddle Buddies, Neonatal-Perinatal Unit, UMass Memorial Health
2024 - Member-at-Large, Executive Board, Industry Exploration Club (IndEx), UMass Chan
2024 - Member, Trainee-Invited Seminar Committee, RTI, UMass Chan
2024 - Co-Chair, Communications Committee, MSTP Student Council, UMass Chan Medical School
2024 - Co-Chair, Community Development Committee, MSTP Student Council, UMass Chan Medical School

2024	Poster Judge, American Physician Scientists Association Northeast Conference
2023 - 2024	Chair, Keynote Speaker Subcommittee, Planning Committee, American Physician Scientists Association Northeast Conference
2023 -	Student Member, Oligonucleotide Therapeutics Society
2023 -	Junior Scientist, RNA Society
2023 -	Member, American Physician Scientists Association
2022 -	Volunteer, ScienceLIVE (science literacy outreach), UMass Chan Medical School
2022 -	Medical Records Volunteer, Boston Marathon, Boston Athletic Association
2021 - 2022	Clinical Volunteer, Vaccine Corps, Commonwealth Health
2021 - 2022	Small-Group Facilitator, Principles of Pharmacology course, UMass Chan Medical School
2021 -	Student Member, Emergency Medicine Residents' Association
2020	Volunteer, COVID-19 Emergency Medical Shelter Program, City of Worcester
2020 -	Clinical Volunteer, Worcester Free Clinic Collaborative
2020 - 2021	Trainee, NIH Ruth L. Kirschstein Institutional National Research Service Award, UMass Chan
2019 -	MD/PhD Candidate, RTI, UMass Chan
2018 - 2019	Emergency Medical Technician, Medical University of South Carolina
2018	Research Assistant, Hamann Lab, Department of Drug Discovery and Biomedical Sciences, College of Pharmacy, Medical University of South Carolina
2017 - 2018	Substitute Teacher, Charleston County School District
2016 -	Student Member, American Chemical Society
2016 - 2017	Research Assistant, Guirgis Lab, Department of Chemistry & Biochemistry, College of Charleston
2016 - 2016	Treasurer, Student Government Association, College of Charleston
2015 - 2017	Student Committeeperson, College of Charleston, Faculty Committee on Academic Standards
2015 - 2015	Research Assistant, Heldrich Lab, Department of Chemistry & Biochemistry, College of Charleston
2014 - 2016	Senator, Student Government Association, College of Charleston

Honors

2023	Poster Award, Oligonucleotide Therapeutics Society Annual Meeting
2023	Travel Award, Oligonucleotide Therapeutics Society
2015 - 2017	LIFE Scholarship with STEM Enhancement, South Carolina Commission on Higher Education
2014 - 2017	President's List Scholar, College of Charleston
2017	Outstanding Student in Chemistry Award, Department of Chemistry & Biochemistry, College of Charleston
2017	HyperCube Scholar Award, HyperCube, Inc.
2017	Departmental Honors, Department of Chemistry & Biochemistry, College of Charleston
2017	Major Field Test Award, Department of Chemistry & Biochemistry, College of Charleston
2016	Summer Undergraduate Research with Faculty Grant, Undergraduate Research and Creative Activities Program, College of Charleston
2015	New Student Leadership Award, Higdon Student Leadership Center, College of Charleston

C. Contribution to Science

Undergraduate Research: The Heldrich Lab designs and optimizes novel organometallic synthetic schemes for organic compounds of interest. Halogenated α,ω-bis(p-anisyl)alkanes are substrates for the Wurtz-Fittig reaction and synthetic intermediates for substituted biarylcyclophanes, a chemical class including clinically relevant natural products like herqulines. Substituted biarylcyclophanes also merit theoretical interest for torsional strain effects and atropisomerism. I successfully performed multi-step synthesis reactions to yield iodinated α,ω-bis(p-anisyl)alkanes of variable lengths, purified crude products by preparative chromatography and recrystallization, and characterized products by mass spectrometry. By preparing a homologous series of halogenated α,ω-bis(p-anisyl)alkanes as model Wurtz-Fittig substrates, my work facilitated optimization of reactions to access desired biarylcyclophanes.

The Guirgis Lab studies the conformational preferences and vibrational modes of novel organometalloid heterocycles, particularly *Si*-substituted silacarbocycles. Such compounds attract theoretical interest for probing the effects of heteroatom position and substituent properties on the observed conformational space via

modulation of steric strain, angle strain, and hyperconjugation. I designed synthetic schemes for five-, six-, and seven-membered silicon heterocycles with diverse substituents, prepared the proposed compounds, purified them, and confirmed their identity with NMR. Additionally, I acquired gas-phase rovibrational spectra for final products via FT-IR spectroscopy. I modeled possible conformers *in silico* and predicted relative stabilities and vibrational modes via MP2/6-31G(d) *ab initio* methods, which Dr. Guirgis correlated with spectral data to identify predominant gas-phase conformers. Our results demonstrated that silicon heterocycles have lower barriers to interconversion of conformers than their carbon analogues and prefer different geometries.

a. Stocka J, Platakyte R, Hickman D, **Carrigan-Broda T**, Ceponkus J, Sablinskas V, Rodziewicz P, Guirgis G. Experimental (Raman and IR) and computational (DFT, MP2) studies of the conformational diversity of 1-chloromethyl-1-fluorosilacyclopentane molecule. *Journal of Molecular Structure*. 2023 January; 1272:134125-.
b. McFadden T, Platakyte R, Stocka J, Ceponkus J, Aleksa V, **Carrigan-Broda T**, Sablinskas V, Rodziewicz P, Guirgis G. Experimental (Raman and IR) and computational (DFT, MP2) studies of conformational diversity of 1-chloromethyl-1-fluorosilacyclohexane. *Journal of Molecular Structure*. 2020 December; 1221:128786-.
c. **Carrigan-Broda TJ**, Guirgis GA. Conformational preferences of silepanes: synthesis, spectroscopic characterization, and ab initio modeling. Colonial Academic Alliance Undergraduate Research Conference; 2017 March; Elon, NC.
d. **Carrigan-Broda TJ**. Conformational preferences of *Si*-substituted silacycloalkanes: synthesis, infrared and NMR spectroscopic characterization, and *ab initio* computational modeling of silepanes and silinanes. Charleston, SC: College of Charleston Honors College; 2017. 43p.

Post-baccalaureate Research: The Hamann Lab studies bioactivity and therapeutic potential of natural products and their chemical derivatives. Manzamine A is a marine natural product demonstrating antimalarial activity *in vitro* and in mice. Chemically modifying manzamine A to incorporate “drug-like” functional groups could improve therapeutic activity and afford characterization of structure-activity relationships. I helped optimize a robust synthetic scheme to systematically derivatize the manzamine A core with diverse aryl groups in lieu of the native carboline substructure. I prepared custom boronate reagents from inexpensive precursors for Suzuki coupling with a halogenated manzamine A core, purified products, and validated their identity via NMR and mass spectrometry. My series of manzamine A analogues allowed subsequent pharmacological screening to identify hits for drug development.

Pre-doctoral Research: The Schiffer Lab studies enzyme inhibitors for antiviral and antibiotic use. The viral protease NS2B-NS3 is essential for maturation of some human flaviviruses; effective NS2B-NS3 inhibitors are therapeutically promising. I synthesized, purified, and characterized a series of novel quinoxaline-based inhibitor candidates designed with fragment-based drug design data. I also expressed, isolated, and quantified NSB2-NS3 from transformed *E. coli*. I screened my compound series for inhibition of NSB2-NS3 using a fluorogenic assay and attempted to co-crystallize a lead inhibitor with NSB2-NS3 for structural studies. My work identified structural criteria for increased potency of quinoxaline-based NSB2-NS3 inhibitors.

The Thompson Lab develops therapeutic strategies against enzymes implicated in disease. Protein arginine deiminases (PADs) mediate dysregulated protein citrullination associated with neurodegenerative and autoimmune disorders. Effects of site-specific citrullination on protein activity are poorly characterized due to limited selectivity of PADs. Biosynthetic methods for producing proteins with defined citrulline-containing sequences may circumvent such limitations. I synthesized, isolated, and characterized citrulline masked with a photocleavable aromatic protecting group. A bioengineered aminoacyl-tRNA synthetase/tRNA pair can recognize the photocleavable aromatic handle in an established genetic code expansion technique, enabling encoding of the masked citrulline in expression constructs using a reassigned stop codon. I confirmed that the citrulline protecting group cleaves under brief UV exposure. I then expressed defined citrullinated proteins in transfected Expi293 cells incubated with the masked citrulline.

The Khvorova Lab specializes in design of therapeutic siRNAs, which mediate sequence-directed gene silencing of pathologic gene products via the RNAi pathway. siRNAs are susceptible to enzyme-mediated inactivation, limiting their therapeutic utility. Under the guidance of Dr. Ken Yamada, I synthesized a library of chemical modifications to the guide strand 5′-end of siRNAs and screened it for metabolic stability *in vitro* and potency *in cellula*. My screens identified several modifications from the 5′-POR class that stabilize siRNA while enhancing potency. I subsequently applied 5′-POR modifications to stabilize anti-microRNA oligonucleotides for anti-neoplastic applications; our collaborators (Krichevsky group, Harvard Medical School) achieved effective reduction of glioblastoma cell viability with our lead anti-microRNA. I prepared lead 5′-POR guide

strands for loading into AGO2 (the principal RNAi effector) *in vitro*; our collaborators (MacRae group, Scripps Institute) determined the structure of the resulting co-crystals, providing useful structure-activity relationship results. Furthermore, I systemically administered lead 5′-POR siRNAs to mice and evaluated efficacy in various extrahepatic tissues, demonstrating tissue-dependent efficacy. My ongoing research includes confirmation of intact 5′-POR siRNA *in cellula* via pulldown experiments, evaluating *in vivo* efficacy of 5’-POR siRNAs with different scaffolds and conjugates, and designing new classes of phosphate-like 5′-end modifications. Manuscripts reporting on these results are in preparation. I expect my research to ultimately improve potency and duration of effect for siRNA drug platforms against numerous diseases.

Carrigan-Broda TJ, Yamada N, Gebert L, Caiazzi J, MacRae I, Yamada K, Khvorova A. Identifying novel siRNA guide strand 5′-end modifications for enhanced chemical stability, potency, and extrahepatic *in vivo* RNAi activity. Oligonucleotide Therapeutics Society Annual Meeting. 2023 October; Barcelona, Spain.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/theodore.carrigan-broda.1/bibliography/public/