BIOGRAPHICAL SKETCH

NAME: Zachary DeBruine

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

POSITION TITLE: Graduate Student

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
Hope College (Holland, MI)	B.S.	08/2011	05/2015	Biochemistry and Molecular Biology
Van Andel Institute Graduate School (Grand Rapids, MI)	Ph.D. (in progress)	08/2015	07/2020 (Est.)	Cellular and Molecular Genetics

A. Personal Statement

My research interests are focused on Wnt pathway signal activation through Frizzled GPCRs, ultimately with the goal of providing strategies for inhibiting the Wnt pathway with improved specificity. My academic training has provided me with excellent opportunities for research, mentoring, collaboration, and professional development. During my undergraduate education I worked part-time in the organic chemistry laboratory of Dr. Moses Lee, then Dean of the Natural and Applied Sciences. I transitioned to work in cell biology with Dr. Maria Burnatowska-Hledin for most of my time as an undergraduate, which resulted in two publications to date and a first-author manuscript currently in progress. Over two years, including two summers, I gained experience in tissue culture, confocal microscopy, many molecular biology techniques, and several biochemical assays. I also worked extensively as a teaching assistant and academic tutor in addition to my studies as a full-time organ performance scholar and managing a start-up business. During this period I was overwhelmed, but from my lack of focus then, I have learned now more than ever to focus while leveraging my diverse background to my advantage. I have transitioned to a period of scientific productivity and am entirely dedicated to a career leading basic science research.

I joined the Van Andel Institute Graduate School immediately after obtaining my undergraduate degree, drawn by an exceptionally collaborative research environment and outstanding faculty. Here I continue to focus intently on major contributions to science. I joined the lab of Dr. Karsten Melcher, working in close collaboration with Dr. Eric Xu and Dr. Bart Williams, all excellent mentors and respected leaders in GPCR biology and Wnt signaling. My ongoing work centers around the structure of a GPCR/ligand/coreceptor complex to be determined by cryo-electron microscopy, though I also incorporate structural genomics and bioinformatics to supplement my structural studies. I have become proficient at a number of molecular biology techniques, including protein expression and purification, cell-based biochemical assays, and operating diverse instruments used in structural biology. I am a trained user on both the Tecnai Spirit and Arctica negative stain and cryo-electron microscopes and have cooperative access to the Titan Krios at the Van Andel Institute.

I thrive in the collaborative environment at the Van Andel Institute, and share expertise with Dr. Bart Williams' lab regularly. I also have reached beyond institutional walls to develop collaborations for more challenging biochemical assays, such as BRET and FCCS, working together with Dr. Gunnar Schulte at the Karolinska Institute and Dr. Lawrence Miller at the Mayo Clinic in Arizona. I value collaborative science and make every effort to develop extensive connections among the Wnt and GPCR community at the annual Wnt conference and GPCR biology conference.

B. Positions and Honors

Positions and Employment

2011 High School Research Assistant in Organic Chemistry (Dr. Moses Lee)
2011 – 2012 Undergraduate Research Assistant in Organic Chemistry (Dr. Moses Lee)
2013 – 2015 Undergraduate Research Assistant in Cell Biology (Dr. Maria Burnatowska-Hledin)
2012 – 2015 Laboratory Teaching Assistant
General Biology I (Vanessa Muilenberg, Ph.D., K. Greg Murray, Ph.D.)

General Biology II (Shana McCrumb, M.S.)
Organismal Biology (Jinshua Li, Ph.D.)
Ecology and Evolutionary Biology (Kathy Winnett-Murray, Ph.D., Shana McCrumb, M.S.)
Advanced Cell Biology (Maria Burnatowska-Hledin, Ph.D.)

2014 Workshop Leader, Ecology and Evolutionary Biology (Greg Murray, Ph.D.)
2014 – 2015 Academic Test Prep Tutor, Cardinal Scholars
2015 Undergraduate Research Assistant in Biochemistry (Karsten Melcher, Ph.D.)
2015 – 2017 Graduate Student Research Fellow (Karsten Melcher, Ph.D.)

Other Experiences and Professional Memberships

2012 – 2016 Member, American Society for Biochemistry and Molecular Biology (ASBMB)
2014 – 2015 President, Biochemistry and Molecular Biology Club, Hope College
2017 – Member, British Pharmacological Society (BPS)
2017 GPCR Pharmacology 2019 Gordon Research Seminar Planning Committee
2017 Origins of Cancer 2018 Symposium Planning Committee
2017 Spectrum Health Office of Research Administration Review Committee

Honors and Awards

2011 High School Summer Research Award in Chemistry, Hope College
2011 – 2015 Presidential Scholarship, Hope College
2011 – 2015 Michigan Competitive Scholarship
2011 – 2015 Ruth Haidt Hughes Memorial Organ Scholarship, Hope College
2011 – 2015 Distinguished Artist Award, Hope College
2013 – 2015 Jaecker-Holleman Chemistry Scholarship, Hope College
2013 Summer Research Award in Biology, Hope College
2014 Summer Research Award in Chemistry, Hope College
2014 – 2015 Dean's List, Hope College
2015 Sigma Xi National Honor Society Nominee
2015 Summer Research Fellowship, Van Andel Institute
2016 EMBO (European Molecular Biology Organization) Travel Award for Wnt 2016 Conference
2017 Outstanding Student Publication Award, Van Andel Research Institute

C. Contributions to Science

My current contributions are focused on determining the structure and function of druggable Wnt pathway targets. I also have a broad range of expertise from my undergraduate and graduate rotation laboratories.

1. **Wnt and Frizzled Structure and Function**. My dissertation research at the Van Andel Institute Graduate School focuses on the structure and function of druggable Wnt pathway receptors and ligands. Under the excellent guidance of Dr. Karsten Melcher, Dr. Eric Xu, and Dr. Bart Williams, I have discovered that Frizzled-4 extracellular cysteine-rich domains dimerize upon lipid engagement, providing a new mechanism for Frizzled drug targeting.[1] This work led to an invited primary-author review in a themed issue of the British Journal of Pharmacology.[2] I presented my work on Frizzled dimerization at multiple conferences, including the Wnt 2016 conference[3] and the GPCR Pharmacology Gordon Research Conference[4], leading to new collaborations, most notably with Dr. Gunnar Schulte of the Karolinska Institute and Michel Bouvier at University of Montreal.

I am currently collaborating with Dr. Ray Stevens and Dr. Fei Xu to functionally characterize a key dimerization interface in FZD_4 based on an unpublished crystal structure, and this work is approaching re-submission to Nature. I have conceived, designed, and am now analyzing a recent study on Frizzled-4 dimerization revealing new requirements for pharmaceutical surrogates of the Wnt pathway, and have developed a personal relationship and collaboration with Dr. Gunnar Schulte with regards to this project. I also maintain active collaborations on this project with Dr. Harikumar Kaleeckal and Dr. Lawrence Miller at Mayo Clinic, AZ. I continue to contribute actively to the Wnt and Frizzled GPCR communities at annual conferences and interact with most of the experts in my field on a personal and regular basis.

1. **DeBruine ZJ**, Ke J, Harikumar KG, Gu X, Borowsky P, Williams BO, Xu W, Miller LJ, Xu HE, Melcher K. Wnt5a promotes Frizzled-4 signalosome assembly by stabilizing cysteine-rich domain dimerization. **Genes and Development**, 2017 May 1;31(9):916-926. Doi: 10.1101/gad.298331.117

2. **DeBruine ZJ**, Xu HE, Melcher K. Assembly and Architecture of the Wnt/β-Catenin Signalosome at the Membrane. **Brit J Pharm**, 2017 Sep 23. Doi: 10.1111/bph.14048 [epub ahead of print].
3. **DeBruine ZJ**, Ke J, Harikumar KG, Miller LJ, Williams BO, Xu HE, Melcher K. Wnt5a promotes Frizzled-4 cysteine-rich domain dimerization. **Wnt 2016 conference**, Brno, CZ. Aug. 2016. *Oral presentation selected from poster abstracts.*
4. **DeBruine ZJ**, Ke J, Harikumar KG, Miller LJ, Xu HE, Melcher K. Frizzled-4 GPCR signalosome assembly is driven by extracellular domain dimerization. **GPCR Pharmacology Gordon Research Conference**, Pisa, IT. Mar. 2017, Oral Presentation.

2. **Epigenetic Regulation of Hemi-methylated DNA.** During a 7-week rotation with Dr. Scott Rothbart at the Van Andel Institute I designed and implemented a novel assay for profiling the substrate selectivity of UHRF1, a regulator of DNA methylation. This work is ongoing under the guidance of Dr. Peter Jones, Dr. Scott Rothbart, and Dr. Rochelle Tiedemann and will be submitted to a high profile journal.

3. **Novel Mechanisms of CUL5 Regulation.** During my third and fourth years at Hope College as an undergraduate, I worked with Dr. Maria Burnatowska-Hledin to identify mechanisms that regulate CUL5 activity. CUL5 is an E3 ubiquitin ligase with high substrate specificity and potent anti-proliferative effect. My main project is the focus of ongoing research nearing publication and submission to JBC or similar. To date I have been involved in two publications from the lab[5,6], and presented posters and oral presentations at multiple conferences and executive events including American Society for Biochemistry and Molecular Biology annual conference[7], National Conference on Undergraduate Research, West Michigan Regional Undergraduate Research Symposium[8], and Hope College Celebration of Undergraduate Research. I was involved in spearheading funding efforts and initial training on a new confocal microscope and gained experience in a wide variety of molecular assays including cloning, Western Blotting, tissue culture, immunocytochemistry, ELISA, and fluorescence-based assays.

5. Kunkler B, Salamango D, **DeBruine ZJ**, Ploch C, Dean S, Hledin M, Marquez G, Madden J, Schnell A, Short M, Burnatowska-Hledin MA. VACM-1/CUL5 is required for thalidomide-dependent inhibition of cellular proliferation. **PLoS Biology**, [re-submitted, will be accepted by my application date].
6. Willis AN, Dean SE, Habbouche JA, Kempers BT, Ludwig ML, Sayfie AD, Lewis SP, Harrier S, **DeBruine ZJ**, Garrett R, Burnatowska-Hledin MA. Nuclear localization signal sequence is required for VACM-1/CUL5-dependent regulation of cellular growth. **Cell Tissue Res**. 2017 Apr;368(1):105-114 doi: 10.1007/s00441-016-2522-7.
7. **DeBruine ZJ**, Breit CM, Burnatowska-Hledin MA. VACM-1/CUL5 nuclear localization is dependent on its NEDD8 post-translational modification status. **National Conference on Undergraduate Research**, Aug. 2013, Oral Presentation.
8. **DeBruine ZJ**, Burnatowska-Hledin MA. VACM-1/CUL5 anti-proliferative effect is regulated by NEDD8 post-translational modification status. **American Society for Biochemistry and Molecular Biology Annual Symposium**, Apr. 2014, Poster Presentation.

4. **Synthesis of DNA Sequence-Specific Polyamide Inhibitors**. My high school senior research internship and first year of undergraduate research was focused around organic synthesis of DNA-binding polyamide inhibitors. This work was not published as the post-docs and mentor moved to industry and decided not follow-up on previous publications.

My bibliography can be viewed here: https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/53324626/