BIOGRAPHICAL SKETCH

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NAME: Ryan Abdella

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POSITION TITLE: CryoEM Facility Manager and Research Assistant Professor

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)*	Completion Date MM/YYYY	FIELD OF STUDY
St. Olaf College, Northfield, MN	B.A.	05/2013	Chemistry
Northwestern University, Evanston, IL	Ph.D.	03/2021	Interdisciplinary Biological Sciences
Howard Hughes Medical Institute, Evanston, IL	Postdoctoral	05/2022	Molecular Biosciences
University of Minnesota, Minneapolis, MN	Postdoctoral	03/2025	Structural Biology/Biochemistry

A. Personal Statement

My research is focused on identifying molecular mechanisms of host-pathogen interactions. I have a long-standing interest in viral replication. I determined a cryoEM structure of the Lassa virus nucleoprotein complex to 1.9 Å (Abdella, et al., *In Preparation*) and am developing assays for trapping viral polymerases during transcription to solve structures at key steps during this process. Another area of interest is the antagonism by herpesvirus proteins of the family of innate immune response proteins called APOBEC3s. In close collaboration with Dr. Hideki Aihara's lab at the University of Minnesota and Dr. Reuben Harris' lab at the University of Texas Health San Antonio, I determined the structures of APOBEC enzymes bound to ribonucleotide reductase subunits from different species of herpesviruses (Abdella, et al., *In Preparation*). This work identified a novel interface used by viral RNRs to bind APOBECs distinct from the interface first identified for Epstein Barr virus Borf2. These RNRs also show diverse cellular localization phenotypes, with some forming stable filaments, that we aim to characterize using cryoET. I have also used these viral RNRs to solve structures of alpaca-derived nanobodies bound to APOBECs using cryoEM, which has revealed both conserved and divergent interfaces between APOBEC3A and APOBEC3B which can be used to develop pan-APOEBEC inhibitors and APOBEC-specific reagents.

As the CryoEM Facility Manager within the Characterization Facility (CharFac) at the University of Minnesota, I am overseeing the installation of new Glacios 2 and Aquilos 2 microscopes scheduled for May 2025. CharFac is located with the College of Science and Engineering and primarily serves users performing materials science research. Therefore, this TP2 proposal will provide me with crucial knowledge to guide the design and implementation of this facility focused on biological TEM to best serve the local research community.

B. Positions, Scientific Appointments, and Honors

Positions

2022-2025 Postdoctoral Associate, University of Minnesota – Twin Cities
2021-2022 Postdoctoral Associate, Northwestern University & Howard Hughes Medical Institute
2018 Guest Lecturer, Department of Molecular Biosciences, Northwestern University

2015-2017 Trainee, Molecular Biophysics Training Program, Northwestern University
2014-2021 Graduate Research Assistant, Northwestern University

Honors

2023-2025 Mentored Project Fellowship, Midwest AViDD Center
2013 Distinction in Chemistry, St. Olaf College
2013 HyperCube Scholar Award, St. Olaf College
2013 Academic Achievement Award, St. Olaf College

Other Experience and Professional Memberships

2020-present Reviewed articles for *Science* and *Nature Communications*
2016 Co-chair of the Northwestern Biophysics Symposium
2015-present Member, Biophysical Society

C. Contributions to Science

1. **Early Career:** My early career contributions were focused on applying my knowledge of chemistry and computer science to understanding how oxidation of methionine residues in calmodulin affects its structure and dynamics. More specifically, I developed molecular dynamics simulations of calmodulin with native methionine residues and oxidated methionine residues to compare to experiments being performed in the lab of David D. Thomas at the University of Minnesota.
    a. **Abdella R,** Thorson D, Moen R, Klein JC, Thomas DD. Site-Specific Methionine Oxidation and Calmodulin Molecular Dynamics. Biophysical Society 56th Annual Meeting; 2012; San Diego, CA.

2. **Graduate Career:** My graduate contributions focused on the transcriptional machinery of paramyxoviruses and human RNA polymerase II. Results from my virology work were highly relevant as they provided evidence of a new conformation of the domains of the viral polymerase responsible for capping and methylating the RNA transcript relative to the polymerase domain. As the polymerase can transcribe messenger RNA, where these enzymatic steps are required, and replicate the genome, where these steps do not occur, my structure provided the first mechanistic understanding for how the polymerase accomplishes both of these processes. For my eukaryotic transcription research, I developed a protocol to assemble a 58-subunit complex on an artificial DNA promoter, allowing for the first high-resolution structure to be determined of a metazoan co-activator Mediator complex bound to the RNA polymerase II-containing pre-initiation complex. This work provided the first structural evidence for Mediator's role in activating an important cell cycle kinase as a critical step during transcription and was published in a major journal.
    a. **Abdella R**, Aggarwal M, Okura T, Lamb RA, He Y. Structure of a paramyxovirus polymerase complex reveals a unique methyltransferase-CTD conformation. Proc Natl Acad Sci U S A. 2020 Mar 3;117(9):4931-4941.
    b. **Abdella R**, Talyzina A, Chen S, Inouye CJ, Tjian R, He Y. Structure of the human Mediator-bound transcription preinitiation complex. Science. 2021 Apr 2;372(6537):52-56.

3. **Postdoctoral Career:** I continued my interest in basic virology which was developed in graduate school by studying Lassa virus replication. Arenaviral genomes are encapsidated by the viral nucleoprotein NP, which has been shown to form trimers during crystallization. I used cryoEM to show that these trimers exist in solution and solved their structure to 1.9 Å resolution, a nearly identical resolution achieved by x-ray crystallography for this sample. I also developed and optimized assays to purify the viral polymerase L on RNA templates to trap specific states during the transcription cycle. I also became interested in studying host-pathogen interactions between the anti-viral APOBEC3 family of cytidine deaminases and herpesvirus ribonucleotide reductase (RNR) proteins. I used a previously characterized RNR, Borf2 from Epstein Barr virus (EBV), to stabilize full-length A3B which is very difficult to solubilize and solved a structure of the complex to 2.5 Å resolution. We learned that the interaction between NTD and CTD of full-length A3B is different than A3G, even with solubilizing mutations made to A3G that mimicked the A3B sequence. Another oncogenic herpes virus, Kaposi's Sarcoma-associated herpes virus, has proven difficult to purify using conventional techniques. We

solubilized a small amount of this protein, formed complexes with A3A and A3Bctd, and collected cryoEM data. From this study, we showed that KSHV Orf61 forms stable filaments *in vitro,* which can bind both APOBECs using a different interface than Borf2, and the resulting filaments differed depending on which APOBEC was bound. We continue to study these filaments in cells using cryoET and work to understand their relevance to herpesvirus replication and infection.

a. **Abdella R,** Aihara H. CryoEM structure of Lassa virus nucleoprotein trimers. In preparation.
b. **Abdella R,** Belica C, Brown W, Carpenter M, Harris R, Aihara H. CryoEM structure of full-length APOBEC3B bound to Epstein Barr virus Borf2. In preparation.
c. **Abdella R,** Belica C, Brown W, Aihara H. CryoEM structures of KSHV Orf61 filaments bound to APOBEC3A and APOBEC3B. In preparation.