BIOGRAPHICAL SKETCH

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NAME: Wade D. Van Horn

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

POSITION TITLE: 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
Brigham Young University, Provo, UT	B.S.	3/2002	Chemistry
University of Utah, Salt Lake City, UT	Ph.D.	8/2007	Chemistry
Vanderbilt University, Nashville, TN	Postdoctoral	6/2012	Biochemistry

A. Personal Statement

Dr. Wade Van Horn was an American Heart Association postdoctoral fellow in the laboratory of Prof. Charles R. Sanders and worked closely with Profs. Alfred L. George and Jens Meiler, where he was trained in membrane protein biophysics and structural studies (Sanders), cell culture and electrophysiology studies (George), and Rosetta-based computational structural biology (Meiler). As a postdoctoral fellow, he was involved in several structural and functional studies, including mechanistic ion channel studies. Dr. Van Horn moved to Arizona State University in 2012 as an assistant professor and was promoted to associate professor in 2018 and to professor in 2024. Dr. Van Horn has successfully recruited outside funding on a variety of projects, including work on understanding the evolution of protein folds (NASA), probing structure and dynamics of non-biological nucleic acids, such as threose nucleic acid (DARPA), and elucidating DNA repair mechanisms (NSF). However, the core focus of his research interest is on membrane protein function, dynamics, and structure. Dr. Van Horn leverages cellular and single-molecule functional studies with cryo-electron microscopy, solution nuclear magnetic resonance (NMR) spectroscopy, and other biophysical and structural techniques. Dr. Van Horn has extensive experience with TRP channels, including the cold-sensing TRPM8 ion channel and the heat sensing TRPV1 ion channel, both are promising targets for therapeutic intervention. As evidenced below, Dr. Van Horn often works on interdisciplinary and collaborative team science and has the experience to carry out the proposed research. In the proposed parent research grant, he collaborates with Dr. Abhishek Singharoy (ASU, Co-I), a computational expert in data sciences, learning methods, and molecular dynamics. Drs. Singharoy and Van Horn have a track record of collaboration; recently they were part of a team that developed the CryoFold software for cryo-EM structural determination and refinement (DOI:https://doi.org/10.1016/j.matt.2021.09.004).The outcomes of the proposed single particle cryo-EM studies are expected to be impactful in unlocking the therapeutic potential of TRPV1 and point towards illuminating receptor mode selectivity.

Ongoing projects that I would like to highlight include:

NIH NINDS R01 NS119505 (PI: Van Horn) 07/01/2022-06/30/2027
Understanding Human TRPV1 Polymodal Activation
Role: PI

NIH NIGMS R35 GM141933 (PI: Van Horn) 05/01/2021-04/30/2026
Molecular Mechanisms and Regulation Networks of TRPM8
Role: PI

NIH NEI R01EY021205 (PI: Lieberman) 03/01/2021 – 02/2/2026
Characterization of Purified Myocilin: Insight into Glaucoma as a Protein Misfolding Disease
Role: Co-PI

NIH NINDS R61 NS127271 (PI: Tidgewell/Kolber) 09/11/2023-08/31/2025
Planning Study for the Development of Sigma 2 Ligands as Analgesics
Role: Co-I

NIH S10OD036204 (PI: Chiu) 09/1/2024-08/31/2025
Electron Energy Filtering System for Cryo-EM Imaging
Role: Co-I

NSF-BIO-DBI 1531991 (PI: Spence) 09/01/2015-08/31/2018
MRI: Acquisition of Cryo-EM for Southwest Regional Center
Role: Co-PI

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2024-	Professor, School of Molecular Sciences, Arizona State University, Tempe, AZ
2018-2024	Associate Professor, School of Molecular Sciences, Arizona State University, Tempe, AZ
2017-	Associate member, Center for Mechanisms of Evolution, Biodesign Institute Arizona State University, Tempe, AZ
2012-	Member, Magnetic Resonance Research Center, Arizona State University, Tempe, AZ
2012-	Member, Virginia G. Piper Center for Personalized Diagnostics, Biodesign Institute Arizona State University, Tempe, AZ
2012-2018	Assistant Professor, School of Molecular Sciences, Arizona State University, Tempe, AZ
2007-2012	Postdoctoral research fellow, Department of Biochemistry, Vanderbilt University School of Medicine, Laboratory of Charles R. Sanders, Nashville, TN
2002-2007	Graduate student, University of Utah Department of Chemistry, Laboratory of Peter F. Flynn, Salt Lake City, Utah

Other Experiences and Professional Memberships

2022-	The Protein Society
2015-	American Society for Biochemistry and Molecular Biology (ASBMB)
2008-	American Association for the Advancement of Science (AAAS) Member
2007-	American Chemical Society Member
2007-	Biophysical Society Member

Honors

2016, 2018	Zebulon Pearce Distinguished Teaching Award Nominee (ASU)
2014-	Biomolecular Structure, Dynamics, and Function: Membrane Proteins Travel Award Recipient (ASU)
2014-	Distinction of Merit and Scholastic Occupation Teaching Award (ASU)
2013-2014	Global Institute of Sustainability Leadership Academy (ASU)
2012-2014	Science Foundation Arizona Early Career Bisgrove Scholar (ASU)
2010-	3rd Annual NIH Roadmap Membrane Protein Technologies Meeting Travel Award Recipient (VU)
2010-2012	American Heart Association Postdoctoral Fellow (VU)
2010-	Cold Spring Harbor-Asia Membrane Proteins Conference Travel Award Recipient (VU)
2007, 2009	NIH Training Grant Fellow in Ion Channel and Transporter Biology (VU)
2006-	University of Utah Graduate School Travel Award Recipient (UU)
2006-	Associated Students of the University of Utah Travel Award Recipient (UU)
2003-2004	NIH Predoctoral Training Grant Fellow in Biological Chemistry (UU)
2003-	Student Representative to the Advisory Council in the Biological Chemistry Program (UU)
2000-	Garth L. Lee Undergraduate Teaching Award Recipient (BYU)

C. Contribution to Science

1. My early publications focused on the application of reverse micelles as fundamental biophysical tools that are broadly compatible with high-resolution solution nuclear magnetic resonance (NMR) studies. I helped to develop reverse micelle technology that was used as mimics for cellular membrane bilayers and

intracellular crowding conditions. The benefit of reverse micelles from a practical spectroscopy perspective is that bulk solution is non-aqueous and generally low viscosity, which allows for enhanced resolution and sensitivity in NMR experiments while the hosted protein is in a fully aqueous environment. These experiments allowed for atomic resolution studies of the effects of crowding and hydration of soluble proteins. Additionally, during these early studies, I was able to adapt reverse micelles, for the first time, as a new type of membrane mimic compatible with high-resolution structural studies of membrane proteins.

a. Van Horn W.D., Ogilvie M.E., Flynn P.F. (2008). Use of reverse micelles in membrane protein structural biology. Journal of Biomolecular NMR, 40(3), 203-211. PMID: 18297402.
b. Van Horn W.D., Ogilvie M.E., Flynn P.F. (2009). Reverse Micelle Encapsulation as a Model for Intracellular Crowding. Journal of the American Chemical Society, 131(23), 8030–8039. PMID: 19469539.
c. Van Horn W.D., Simorellis A.K., Flynn P.F. (2005). Low Temperature Studies of Encapsulated Proteins. Journal of the American Chemical Society, 127(39), 13553-13560. PMID: 16190719.
d. Simorellis A.K., Van Horn W.D., Flynn P.F. (2006). Dynamics of Low Temperature Induced Water Shedding from AOT Reverse Micelles. Journal of the American Chemical Society, 128(15), 5080-5090. PMID: 16608342.

2. The development of membrane protein tools described above captured my interest in membrane protein structure, dynamics, and function. In this contribution, I became focused on the critical and diverse roles that membrane proteins play in health and disease. I also became adept at membrane protein handling and NMR-based structure determination. These studies included structure determination of biomedically relevant membrane proteins and further development and assessment of techniques and membrane mimics which has continued throughout my studies.
    a. Barrett P.J., Song Y., Van Horn W.D., Hustedt E.J., Schafer J.M., Hadziselimovic A., Beel A.J., Sanders C.R. (2012). The amyloid precursor protein has a flexible transmembrane domain and binds cholesterol. Science. 336(6085), 1168-1171. PMCID: PMC3528355.
    b. Van Horn W.D., Kim H., Ellis C.D., Hadziselimovic A., Sulistijo E.S., Karra M.D., Tian C., Sönnichsen F.D., Sanders C.R. (2009). NMR Solution Structure of the Membrane-Integral Diacylglycerol Kinase. Science. 324(5935), 1726-1729. PMCID: PMC2764269.
    c. Lu Z., Van Horn W.D., Chen J., Mathew S., Zent R., Sanders, C.R. (2012). Bicelles at low concentrations, Molecular Pharmaceutics 2012, 9(4), 752-761. PMCID: PMC3319193.
    d. Hutchison J.M. Capone R., Luu D.D., Shah K.H., Hadziselimovic A., Van Horn W.D., Sanders C.R. (2021). Recombinant SARS-CoV-2 envelope protein traffics to the trans-Golgi network following amphipol-mediated delivery into human cells. J. Biol. Chem. 297(2), 100940-100940. PMCID: PMC8256659.

3. Through the previous studies highlighted above, I became familiar with and interested in ion channel structure, dynamics, function, and regulation. Currently, this is the primary focus of my laboratory, investigating the interplay between structure and dynamics and its roles on function and disease. We mix functional, structural, and computational studies to probe fundamental questions in ion channel gating and regulation. These studies have included voltage-gated potassium channels involved in cardiac repolarization and the role of sex hormones in ion channel regulation. Currently, we are pursuing studies of transient receptor potential (TRP) ion channels and the mechanisms of polymodal regulation, including how ligands interact and activate these biologically and pharmacologically important receptors.
    a. Kim M., Sisco N.J., Hilton J.K., Montano C.M., Castro M.A., Cherry B.R., Levitus M., Van Horn W.D.* (2020) Evidence that the TRPV1 S1-S4 membrane domain contributes to thermosensing. Nature Communications, 11, 4169. PMCID: PMC7441067.
    b. Sisco N.J., Helsell C.V.M., Van Horn W.D.* (2019) Competitive Interactions between PIRT the Cold Sensing Ion Channel TRPM8, and PIP_2 Suggest a Mechanism for Regulation. Scientific Reports, 9, 14128. PMCID: PMC6773951.
    c. Hilton J.K., Salehpour, T., Sisco N.J., Rath P., Van Horn W.D.* (2018). Phosphoinositide-interacting regulator of TRP (PIRT) has opposing effects on human and mouse TRPM8 ion channels. Journal of Biological Chemistry. 293(24), 9423-9434. PMCID: PMC6005438.
    d. Rath P., Hilton J.K., Sisco N.J., Van Horn W.D.* (2016). Implications of Human Transient Receptor Potential Melastatin 8 (TRPM8) Channel Gating from Menthol Binding Studies of the Sensing Domain. Biochemistry. 55(1), 114-124. PMCID: PMC4865251.

4. In addition to my long-standing interest in ion channels and membrane proteins in general, I have broad biophysical interests that span nucleic acids and proteins. These include structural and biophysical studies of artificial genetic polymers, which are relevant to synthetic biology and have potential applications as a novel class of therapeutics. In particular, I have been studying threose nucleic acid (TNA), a xeno-nucleic acid, with a sugar-phosphate backbone that differs from the biological genetic polymers, DNA and RNA. We have been using an array of techniques to understand the thermodynamic, structural, and dynamic consequences of the differences in backbones and the molecular details of TNA/DNA and TNA/RNA Watson-Crick heteroduplexes. This has led us more recently into the field of biological nucleic acid studies, where we are working to define the dynamics and thermodynamics that underlie the early stages of DNA repair. As a natural extension of our interests in biomolecular dynamics, we are also collaboratively studying NMR-based protein dynamics across various systems.
    a. Anosova I., Kowal E.A., Sisco N.J., Sau S., Liao J., Bala S., Rozners E., Egli M., Chaput J.C., Van Horn W.D*. (2016). Structural Insights into Conformational Differences between DNA/TNA and RNA/TNA Chimeric Duplexes. ChemBioChem. 17(18), 1705-1708. PMCID: PMC5242226.
    b. Modi T., Risso V.A., Martinez-Rodriguez S., Gavira J.A., Mebrat M.D., Van Horn W.D., Sanchez-Ruiz J.M, Ozkan S.B. (2021). Hinge-shift mechanism as a protein design principle for the evolution of β-lactamases from substrate promiscuity to specificity. Nature Communications. 12, 1852. PMCID: PMC7994827.
    c. Orndorff P.B., Poddar S., Owens A.M., Kumari N., Ugaz B.T., Amin S., Van Horn W.D., van der Vaart A., Levitus M. (2023) Uracil-DNA glycosylase efficiency is modulated by substrate rigidity. Scientific Reports. 13, 3915. PMCID: PMC9995336.
    d. Saccuzzo E.G., Mebrat M.D., Scelsi H.F., Kim M., Ma M.T., Su X., Hill S.E., Rheaume E., Li R., Torres M.P., Gumbart J.C., Van Horn W.D., Lieberman R.L. (2024). Competition between inside-out unfolding and pathogenic aggregation in an amyloid-forming β-propeller. Nature Communications. 15, 155. PMCID: PMC10762032.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1tE0gmWB11Skm/bibliography/49020049/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Lopez, Kyle E.

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

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
University of Arizona	BS	08/2013	05/2017	Biochemistry and Cellular & Molecular Biology
University of California, San Francisco	PHD	09/2017	06/2022	Biophysics
Arizona State University	Postdoctoral Fellow	07/2022	Present	Biophysics and Structural Biology

A. Personal Statement

Throughout my academic career I've acquired expertise in key disciplines that are beneficial for the proposed project which includes biochemistry, molecular biology, biophysics, and structural biology. I conducted undergraduate research with Dr. William Montfort where I studied conformational dynamics of a protein involved in vasodilation in response to small molecules in collaboration with Ironwood Pharmaceuticals. Additionally, I did a summer internship in Dr. Doug Rees' lab at Caltech, where I crystallized a membrane protein methionine transporter in bacteria. I attempted to determine structures of the complex in various conformations in the transportation mechanism. In graduate school, I studied the highly dynamic AAA family of proteins in Dr. Daniel Southworth's lab. I used cryo-electron microscopy (cryoEM) to uncover the mechanism of how the bacterial AAA protein ClpA couples substrate unfolding to proteolysis at its cognate protease ClpP[1]. To further understand this process, I determine low resolution structures of the complex bound to an adaptor protein that delivers a different class of substrates. Furthermore, I developed a collaborative project with Dr. Jason Sello at UCSF and Karl Schmitz at the University of Delaware to improve a class of potential tuberculosis antibiotics that target the Clp system I studied. I used cryoEM to determine where these molecules bound and the mechanism of action[2]. I recently joined Dr. Van Horn's group at Arizona State University, and I plan to use my expertise in cryoEM to study the human TRPV1 channel and how it responds to stimuli at a molecular level. I also plan to gain expertise in cellular biology techniques such as cell imaging and patch clamp to functionally test hypotheses generated from TRPV1 molecular structures. My long-term research goals are to run my own academic research lab that studies the interactions between molecular chaperones and essential cell signaling proteins such as TRPV1. Learning how to purify and handle membrane proteins for cryoEM in the Van Horn lab will be crucial in developing my own research lab. In addition, experience with mammalian cell culture and electrophysiology techniques to test ion channel function will be important if I study how chaperones modulate the function of channels.

1. **Lopez K. E.*,** Rizo A. N.*, Tse E., Lin J., Scull N. W., Thwin A. C., Lucius A. L., Shorter J., Southworth D. R. Conformational plasticity of the ClpAP AAA+ protease couples protein unfolding and proteolysis. *Nature Structural and Molecular Biology.* 2020; 27:406-416
2. **Lopez K. E.,** Burnside C., Prorok M., Fei F., Tse E., Sello J. K., Schmitz K. R., Southworth D. R. Structural basis of an acyldepsipeptide fragment stimulation of *Mycobacterium tuberculosis* protease ClpP1P2 activity. *Proceedings of the National Academy of Sciences.* (In preparation).

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2025-present	Arizona State University Presidential Postdoctoral Fellowship
2023-2025	American Heart Association Postdoctoral Fellowship
2022-present	Postdoctoral Researcher, Arizona State University
2020-2021	Integrated Program in Complex Biological Systems T32, UCSF
2019-2022	Discovery Graduate Fellow, UCSF
2017-2022	Graduate Research Assistant, UCSF
2016	Southern California Edison WAVE Undergraduate Fellow, Caltech
2015-2017	Maximizing Access to Research Careers (MARC) Scholar, University of Arizona
2014-2015	Native American Cancer Prevention (NACP) Trainee, University of Arizona

Honors

2017	B.S. awarded with honors, University of Arizona
2016	Michael A. Wells Undergraduate Research Endowment, University of Arizona
2016	Annual Biomedical Research Conference for Minority Students (ABRCMS) Poster Award
2015	Biophysical Society Travel Award
2015	American Society for Biochemistry and Molecular Biology (ASBMB) Regional Travel Grant
2013-2017	Presidential Tuition Scholarship, University of Arizona

C. Contributions to Science

1. **Early Career:** Early in my research career my contributions were aimed at understanding the conformational dynamics of soluble guanylate cyclase (sGC) when bound to various vasodilating small molecules. I used lanthanide resonance energy transfer (LRET) to measure intramolecular distances in sGC in response to small molecule binding. I also tried to determine the sGC molecular structure via X-ray crystallography, but the dynamic nature of the protein made this difficult. This work was continued by an incoming graduate student in the lab and is still on-going. Additionally, in Dr. Doug Rees' lab I isolated several nanobodies that bind to the bacterial methionine importer MetNI and inhibit function. These were used for subsequent crystallography studies to determine the inward facing conformation of the MetNI transporter.
2. **Graduate Career:** My graduate research contributed to our understanding of the ClpAP substrate processing mechanism and how small molecules perturb this system. My publication on the *E. coli* ClpAP system[a] proposes a novel mechanism for how the system couples substrate unfolding to proteolysis and the model is shown to be similar in homologous Clp systems. In addition, I cloned and developed a purification protocol for the ClpAP adaptor protein ClpS and a degron tagged GFP substrate that binds ClpS. With these purified components, I determine initial, low resolution electron density maps of the ClpAPS-degron tagged substrate complex. Through complex cryoEM data processing techniques, I determined the translocation mechanism proposed in my previous publication[a] is also used when ClpS delivers different classes of substrates. Finally, I determined high resolution cryoEM structures of *M. tuberculosis* ClpP1P2 protease bound to an small molecule that stimulates its activity[b]. These structures revealed the mechanism of stimulation and allowed our collaborators to synthesis more potent compounds that will potentially be used as antibiotics. Additionally, I was involved in a collaborative effort as a member of the Quantitative Biosciences Institute Coronavirus Research Group Structural Biology Consortium at UCSF to develop and determine structures of neutralizing SARS-CoV-2 antibodies using cryoEM[c]. In this work I collected and processed cryoEM data of spike protein bound to a number of antibody complexes.

a. **Lopez K. E.*,** Rizo A. N.*, Tse E., Lin J., Scull N. W., Thwin A. C., Lucius A. L., Shorter J., Southworth D. R. Conformational plasticity of the ClpAP AAA+ protease couples protein unfolding and proteolysis. *Nature Structural and Molecular Biology.* 2020; 27:406-416
b. **Lopez K. E.,** Burnside C., Prorok M., Fei F., Tse E., Sello J. K., Schmitz K. R., Southworth D. R. Structural basis of an acyldepsipeptide fragment stimulation of *Mycobacterium tuberculosis* protease ClpP1P2 activity. (In preparation).
c. Schoof M.*, Faust B.*, Saunders R. A.*, Sangwan S.*, Rezelj V.*,…,**Lopez K. E.**,…, Walter P., Manglik A. An ultrapotent synthetic nanobody neutralizes SARS-CoV-2 by stabilizing the inactive spike. *Science.* 2020; 370:1473-1479.

3. **Postdoctoral Career:** I recently started my postdoctoral career in Dr. Wade Van Horn's lab and I have already successfully purified a human TRPV1 construct that contains the transmembrane domain which is shown to form tetramers and respond to heat stimulus. I processed negative stain data of the transmembrane domain in nanodisc to confirm tetramer formation and the overall molecular envelope of the complex. Additionally, I collected a cryoEM dataset on a TRP channel isoform and established myself in the cryoEM community at ASU. I plan to study the mechanism of TRPV1 heat and agonist activation during my time as a postdoctoral fellow. I aim to learn how to handle membrane proteins, how to prepare membrane mimics, mammalian cell culture and electrophysiology techniques as a post-doctoral fellow.

Complete List of Published Work in my Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/kyle.lopez.1/bibliography/public/

D. Scholastic Performance

YEAR	COURSE TITLE	GRADE
	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	
2017,2018	Critical Topics in Biomedical Informatics	S
2017	Macromolecular Structure and Interaction Methods	A
2017	Physical Underpinnings of Biological Systems	A
2017-2022	Biophysics Seminar	S
2017	Scientific Writing: applying for the NSF predoctoral fellows	A
2018	Macromolecular Structure and Interactions	A
2018	Molecular Thermodynamics	A
2018	Special Topics in Virology	S
2018	Special Topics in CRISPR/Cas9 Biology	S
2018	Special Topics in Cryo-Electron Microscopy	S
2019	Ethics and the Responsible Conduct of Research	S

Courses that are pass fail are graded as S (Satisfactory) or NS (Non-satisfactory) otherwise they are graded on the canonical A-F scale.