

BIOGRAPHICAL SKETCH

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NAME: Acharya, Priyamvada

eRA COMMONS USER NAME (credential, e.g., agency login): Acharya001

POSITION TITLE: Associate 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
Jadavpur University, Kolkata, India	BSc	06/1994	Chemistry
Jadavpur University, Kolkata, India	MSc	06/1996	Organic Chemistry
Center for Cellular and Molecular Biology, Hyderabad, India	PhD	09/2003	Biochemistry

A. Personal Statement

The primary focus of my research at Duke University is to understand structural details of viral entry and interactions of viral surface proteins with the host immune system. Combining these two intersecting areas of basic research, my laboratory interfaces with teams of virologists, immunologists, and computational biologists to leverage our atomic level findings for vaccine and therapeutics development. As Director of the Division of Structural Biology, Duke Human Vaccine Initiative (DHVI), I lead the structural biology program at DHVI. My laboratory leads several NIH-funded research programs, including the **Duke Center for HIV-1 Structural Biology (DCHSB)**, one of six HIV structural biology centers funded by the National Institute of Allergy and Infectious Diseases (NIAID). The DCHSB is focused on the HIV-1 Env investigating topics covering HIV-1 entry and fusion, Env-initiated immune activation of B cell receptors, and the role of anti-Env antibodies in blocking viral rebound. My research group at Duke has established robust structural determination pipelines leveraging cryo-EM and x-ray crystallography, and combining these with biochemical and biophysical techniques, we have gained atomic level information into the HIV-1 Envelope (Env), SARS-CoV-2 spike, and Henipavirus fusion proteins, that have yielded key insights into their function and mechanisms.

My team's success in utilizing atomic level structures across virus families to inform basic biology and the impact of our highly collaborative and multidisciplinary research program in contributing fundamental insights into virology is highlighted by the following three publications:

- Williams WB*, Meyerhoff RR, Edwards RJ, Li H, Manne K, Nicely NI, Henderson R, Zhou Y, Janowska K, Mansouri K, Gobeil S, Evangelous T, Hora B, Berry M, Abuaahmad AY, Spreng J, Deyton M, Stalls V, Kopp M, Hsu AL, Borgnia MJ, Stewart-Jones G, Lee MS, Bronkema N, Moody MA, Wiehe K, Bradley T, Alam SM, Parks RJ, Foulger A, Oguin T, Sempowski GD, Bonsignori M, LaBranche CC, Montefiori DC, Seaman M, Santra S, Perfect J, Francica JR, Lynn GM, Aussedat B, Walkowicz WE, Laga R, Kelsoe G, Saunders KO, Fera D, Kwong PD, Seder RA, Bartsaghi A, Shaw GM, **Acharya P**, Haynes BF. (2021) Fab-dimerized glycan-reactive antibodies are a structural category of natural antibodies. *Cell*, May 2021, 184, 2955.
- May AJ, Pothula KR, Janowska K, **Acharya P**. (2023) Structures of Langya virus fusion protein ectodomain in pre and post fusion conformation. *J Virol* (in press).
- Gobeil SM, Janowska K, McDowell S, Mansouri K, Parks R, Stalls V, Kopp MF, Manne K, Saunders K, Edwards RJ, Haynes BF, Henderson RC, **Acharya P**. Effect of natural mutations of SARS-CoV-2 on spike structure, conformation, and antigenicity. *Science* Aug 2021, eabi6226. doi: 10.1126/science.abi6226. Epub 2021 Jun 24.

Ongoing and recently completed projects that I would like to highlight include:

U54 AI170752 (PI: Acharya)

6/14/2022 - 3/31/2027

NIH

Duke Center for HIV Structural Biology.

R01 AI145687 (PI: Acharya)

02/01/2019 – 01/31/2024

NIH

Structures of initial CD4 engagement with pre-fusion, closed HIV-1 Envelope trimer and early CD4-induced conformational changes required for infection.

R01 AI165147 (PI: Acharya)

09/01/2021 – 08/31/2026

NIH

Structural characterization of Fab-dimerized glycan-reactive antibodies that neutralize HIV-1.

R01AI165947 (PI: Acharya)

02/01/2023 – 01/31/2027

NIH

Effect of natural and engineered variations on structure and biophysics of SARS-CoV-2 spike.

R01 AI145687-02S1 (PI: Acharya)

05/21/2020 – 01/31/2022

NIH

Targeting early metastable intermediates of the SARS-CoV-2 spike for vaccine and therapeutics development.

R21AI150415 (PI: Acharya)

01/09/2020 - 12/31/2021

NIH

Structure and dynamics of a functional cavity in the HIV-1 Envelope, and its role in conformational changes required for infection.

B. Positions, Scientific Appointments and Honors

Positions and Employment

2003-2005 Visiting Scientist, Max Planck Institute of Biophysics, Frankfurt, Germany, and Max Planck Institute for Terrestrial Microbiology, Marburg, Germany
2005-2009 Visiting Fellow, Structural Biology Section (SBS), Vaccine Research Center (VRC), National Institutes of Allergy and Infectious diseases (NIAID), National Institutes of Health (NIH), Bethesda, Maryland, USA
2009-2013 Research Fellow, SBS/VRC/NIAID/NIH, Bethesda, Maryland, USA
2013-2015 SBS/VRC/NIAID/NIH Bethesda, Maryland, USA
2015-June 29, 2018 Research Scientist, Simons Electron Microscopy Center (SEMC), New York Structural Biology Center (NYSBC), New York, and SBS/VRC/NIAID/NIH, Bethesda, Maryland, USA
July 1, 2018- present- Associate Professor and Director of Structural Biology, Duke Human Vaccine Institute, Department of Surgery, Duke School of Medicine, Durham, NC, USA

Honors

1997 Junior Research Fellowship, Council of Scientific and Industrial Research (CSIR), India
1999 Senior Research Fellowship, CSIR, India
2017 Robert P. Apkarian Memorial Scholarship, Microscopy and Microanalysis Meeting
2017 Distinguished Achievement Award, NIH/Kelly Government Solutions
2018 Distinguished Achievement Award, NIH/Kelly Government Solutions
2018 Young Faculty Award, Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (Duke-CHAVD)
2018 Translating Duke Health Initiative (TDHI) Scholar
2019 Outstanding Achievement Award, Duke-CHAVD, Duke University.
2020 Young Faculty Award, Duke-CHAVD, Duke University.
2022 Norman L. Letvin Duke CHAVD Scholar Award, Duke University.

C. Contributions to Science

1. **Structural biology of HIV-1 entry and its application to vaccine and therapeutics design.** Working to decipher the mechanism of HIV-1 entry, I combined X-ray crystallography and NMR to determine the structure of CCR5 N terminus bound to HIV-1 Env. Combining structural information with a high-throughput binding assay I discovered small molecule mimetics of the CCR5 N terminus that inhibited entry of diverse HIV-1 strains. I led structural investigations in a multi-institutional collaboration to develop a highly potent HIV-1 entry inhibitor M48U1 and solved the structure of M48U1 bound to HIV-1 gp120 at 1.5 Å resolution. This is the highest resolution structure determined for an HIV-1 Env complex to date. Utilizing basic knowledge of structural biology of HIV-1 entry towards vaccine design, I developed HIV-1 Env variants that are not susceptible to CD4-induced opening. Among these is DS-SOSIP – an Env construct stabilized by disulfides designed to resist CD4-induced structural changes. DS-SOSIP is widely used in the field for vaccine studies.
 - a. **Acharya P**, Dogo-Isonagie C, LaLonde JM, Lam SN, Leslie GJ, Louder MK, Frye LL, Debnath AK, Greenwood JR, Luongo TS, Martin L, Watts KS, Hoxie JA, Mascola JR, Bewley CA, Kwong PD. **Structure-based identification and neutralization mechanism of tyrosine sulfate mimetics that inhibit HIV-1 entry.** *ACS Chemical Biol*, 6(10):1069-1077, Oct 2011. PMID: PMC2650494
 - b. Liu Q§, **Acharya P§**, Dolan MA, Zhang P, Guzzo C, Lu J, Kwon A, Gururani D, Miao H, Bylund T, Chuang GY, Druz A, Zhou T, Rice W, Wigge C, Carragher B, Potter CS, Kwong PD, Lusso P. **Structure and functional characterization of the initial quaternary contact of CD4 with the HIV-1 envelope trimer.** *Nat Struc Mol Biol*, Apr 2017, 24(4):370-378. PMID: PMC5798227 (§ Co-first author).
 - c. **Acharya P**, Luongo TS, Louder MK, McKee K, Yang Y, Do Kwon Y, Mascola JR, Kessler P, Martin L, Kwong PD. **Structural basis for highly effective HIV-1 neutralization by CD4-mimetic miniproteins revealed by 1.5 Å cocrystal structure of gp120 and M48U1.** *Structure*, Jun 2013, 21(6):1018-1029. PMID: PMC4140785
 - d. Henderson R, Lu M, Zhou Y, Mu Z, Parks R, Han Q, Hsu AL, Carter E, Blanchard SC, Edwards RJ, Wiehe K, Saunders KO, Borgnia MJ, Bartesaghi A, Mothes W, Haynes BF, **Acharya P**, Munir Alam S. **Disruption of the HIV-1 Envelope allosteric network blocks CD4-induced rearrangements.** *Nat Commun.*, Jan 2020, 11(1):520. doi: 10.1038/s41467-019-14196-w. PMID: PMC6981184
2. **Structural basis of broad antibody mediated HIV-1 neutralization.** I led several studies to elucidate epitopes of broadly neutralizing antibodies and the mechanism of breadth acquisition. Studying HIV-1 neutralizing antibodies derived from the VH1-46 heavy chain germline, I demonstrated a mode of binding distinct from the VRC01-class that derived from the VH1-2 germline. In work done after I moved to DHVI as the Director of the Division of Structural Biology, my team determined the structure of the unmutated common ancestor of the CD4-binding site antibody lineage CH235, in complex with an Env immunogen. Recently, my team determined structures of antibodies in complex with HIV-1 Env for all observed members and ancestral states of the broadly neutralizing HIV-1 V3-glycan targeting DH270 antibody clonal B cell lineage. These structures tracked the development of neutralization breadth from the unmutated common ancestor to define affinity maturation at high spatial resolution, identified bottlenecks on the path to natural affinity maturation and revealed solutions that will inform immunogen design aimed at eliciting a broadly neutralizing immune response by vaccination.
 - a. LaBranche CC, Henderson R, Hsu A, Behrens S, Chen X, Zhou T, Wiehe K, Saunders KO, Alam SM, Bonsignori M, Borgnia MJ, Sattentau QJ, Eaton A, Greene K, Gao H, Liao HX, Williams WB, Peacock J, Tang H, Perez LG, Edwards RJ, Kepler TB, Korber BT, Kwong PD, Mascola JR, **Acharya P**, Haynes BF, Montefiori DC. **Neutralization-guided design of HIV-1 envelope trimers with high affinity for the unmutated common ancestor of CH235 lineage CD4bs broadly neutralizing antibodies.** *Plos Pathog.*, Sep 2019, 15(9):e1008026. doi: 10.1371/journal.ppat.1008026.
 - b. Saunders KO, Edwards RJ, Tilahun K, Manne K, Lu X, Cain DW, Wiehe K, Williams WB, Mansouri K, Hernandez GE, Sutherland L, Searce R, Parks R, Barr M, DeMarco T, Eater CM, Eaton A, Morton G, Mildenberg B, Wang Y, Rountree RW, Tomai MA, Fox CB, Moody MA, Alam SM, Santra S, Lewis MG, Denny TN, Shaw GM, Montefiori DC, **Acharya P**, Haynes BF. **Stabilized HIV-1 envelope immunization induces neutralizing antibodies to the CD4bs and protects macaques against mucosal infection.** *Sci Transl Med.*, Sep 2022, 14(661):eabo5598. doi:10.1126/scitranslmed.abo5598. Epub 2022 Sep 7.

- c. Henderson R, Zhou Y, Stalls V, Wiehe K, Saunders KO, Wagh K, Anasti K, Barr M, Parks R, Alam SM, Korber B, Haynes BF, Bartesaghi A, **Acharya P.** (2023) **Structural basis for breadth development in the HIV-1 V3-glycan targeting DH270 antibody clonal lineage.** *Nat Commun.*, May 2023;14(1):2782. doi: 10.1038/s41467-023-38108-1.
 - d. Saunders KO, Counts J, Thakur B, Stalls V, Edwards R, Manne K, Lu X, Mansouri K, Chen Y, Parks R, Barr M, Sutherland L, Bal J, Havill N, Chen H, Machiele E, Jamieson N, Hora B, Kopp M, Janowska K, Anasti K, Jiang C, Van Itallie E, Venkatayogi S, Eaton A, Henderson R, Barbosa C, Alam SM, Santra S, Weissman D, Moody MA, Cain DW, Tam YK, Lewis M, Williams WB, Wiehe K, Montefiori DC, **Acharya P**, Haynes BF. (2024) **Vaccine induction of CD4-mimicking HIV-1 broadly neutralizing antibody precursors in macaques.** *Cell*, 187(1):79-94.
3. **Vaccine development targeting the HIV-1 Env fusion peptide.** I led mechanistic investigations and cryo-EM structural determination of antibodies that target the HIV-1 Env fusion peptide. These structure-function studies revealed distinct modes of antibody recognition of the fusion peptide and revealed the structural determinants of resistance to fusion peptide directed antibodies.
- a. Kong R, Xu K, Zhou T, **Acharya P**, Lemmin T, Liu K, Ozorowski G, Soto C, Taft JD, Bailer RT, Cale EM, Chen L, Choi CW, Chuang GY, Doria-Rose NA, Druz A, Georgiev IS, Gorman J, Huang J, Joyce MG, Louder MK, Ma X, McKee K, O'Dell S, Pancera M, Yang Y, Blanchard SC, Mothes W, Burton DR, Koff WC, Connors M, Ward AB, Kwong PD, Mascola JR. **Fusion peptide of HIV-1 as a site of vulnerability to neutralizing antibody.** *Science*, May 2016, 352(6287):828-833. PMID: PMC4917739
 - b. Kai X\$, **Acharya P**\$, Kong R\$, Cheng Cheng\$, Chuang G, Liu K, Louder MK, O'Dell S, Rawi R, Sastry M, Shen C, Zhang, B, Zhou T, Asokan M, Bailer RT, Chambers M, Chen X, hoi CW, Dandey VP, Doria-Rose N, Druz A, Eng ET, Farney K, Foulds KE, Geng H, Georgiev IS, Gorman J, Hill KR, Jafari AJ, Kwon YD, Lai YT, Lemmin T, McKee K, Ohr TY, Ou L, Peng D, Roshan AP, Sheng Z, Todd JP, Tsybovsky Y, Viox EG, Wang Y, Wei H, Yang Y, Zhou AF, Chen R, Yang L, Scorpio DG, McDermott AB, Shapiro L, Carragher B, Potter CS, Mascola JR, Kwong PD. **Epitope-based vaccine design yields fusion peptide-directed antibodies that neutralize diverse strains of HIV-1.** *Nat Med*, 24(6):857-867, June 2018 (§ Co-first author)
 - c. Dingens AS\$, **Acharya P**\$, Haddox HK, Rawi R, Xu K, Chuang G, Wei H, Mascola JR, Carragher B, Potter CS, Overbaugh J, Kwong PD, Bloom, JD. (2018) **Epitope-based vaccine design yields fusion peptide-directed antibodies that neutralize diverse strains of HIV-1.** *Plos Pathogens*, Jul 2018, 14(7):e1007159. (§ Co-first author)
 - d. Kong R\$, Duan H\$, Sheng Z\$, Xu K\$, **Acharya P**\$, Chen X\$, Cheng C\$, Dingens AS\$, Gorman J\$, Sastry M\$, Shen CH\$, Zhang B\$, Zhou T\$, Chuang GY, Chao CW, Gu Y, Jafari AJ, Louder MK, O'Dell S, Rowshan AP, Viox EG, Wang Y, Choi CW, Corcoran MM, Corrigan AR, Dandey VP, Eng ET, Geng H, Foulds KE, Guo Y, Kwon YD, Lin B, Liu K, Mason RD, Nason MC, Ohr TY, Ou L, Rawi R, Sarfo EK, Schön A, Todd JP, Wang S, Wei H, Wu W; NISC Comparative Sequencing Program, Mullikin JC, Bailer RT, Doria-Rose NA, Karlsson Hedestam GB, Scorpio DG, Overbaugh J, Bloom JD, Carragher B, Potter CS, Shapiro L, Kwong PD, Mascola JR. **Antibody Lineages with Vaccine-Induced Antigen-Binding Hotspots Develop Broad HIV Neutralization.** *Cell*, July 2019, 178(3):567-584, (§ Co-first author)
4. **Structural determination of ADCC mediating antibodies.** Determined the structure of A32-like antibody 2.2c in complex with HIV-1 gp120. A32-like antibodies target the gp41-interactive region of gp120 at its N terminus and become exposed on the surface of the native Env spike at the later stages of viral entry following receptor engagement. Determined structures of other A32-like antibodies, studies from which we were able to glean insights into the recognition of antibodies that mediate potent antibody-dependent cellular cytotoxicity (ADCC).
- a. **Acharya P**, Tolbert WD, Gohain N, Wu X, Yu L, Liu T, Huang W, Huang CC, Do Kwon Y, Louder RK, Luongo TS, McLellan JS, Pancera M, Yang Y, Zhang B, Flinko R, Foulke JS Jr, Sajadi MM, Kamin-Lewis R, Robinson JE, Martin L, Kwong PD, Guan Y, DeVico AL, Lewis GK, Pazgier M. **Structural Definition of an Antibody-Dependent Cellular Cytotoxicity (ADCC) Response Implicated in Reduced Risk for HIV-1 Infection.** *J Virol*, Aug 2014, 88(21):12895-12906. PMID: PMC4248932
 - b. Gohain N, Tolbert WD, **Acharya P**, Yu L, Liu T, Zhao P, Orlandi C, Visciano ML, Kamin-Lewis R, Sajadi MM, Martin L, Robinson JE, Kwong PD, DeVico AL, Ray K, Lewis GK, Pazgier M. **Cocrystal**

5. **Structural biology of the SARS-CoV-2 spike and its application to vaccine design.** During the early months of the COVID-19 pandemic, my research group pivoted to apply our expertise and skills in studying the structural biology of HIV-1 entry to research on the SARS-CoV-2 spike (S). We rapidly established methods for purification, and biochemical and biophysical characterization of the SARS-CoV-2 S. Doing so, we discovered unusual cold sensitivity of the S protein, wherein the spike ectodomain is destabilized by cold temperature storage, an effect that could be reversed by incubation at 37 °C or by stabilizing its conformation in the 'down' state. Collaborating with Dr. Henderson, we applied vector analysis to CoV spikes and defined mutations that would stabilize discrete spike conformations. Thus, we developed two novel spikes, one locked in the all-RBD-down conformation, and the other with higher proportion of the up-RBD forms. We determined structures of the S ectodomain with the D614G mutation and showed that the D614G mutation alters RBD positioning and increase furin cleavage at the S1/S2 junction.
- Gobeil SM, Henderson R, Stalls V, Janowska K, Huang X, May A, Speakman M, Beaudoin E, Manne K, Li D, Parks R, Barr M, Deyton M, Martin M, Mansouri K, Edwards RJ, Sempowski GD, Saunders KO, Wiehe K, Williams W, Korber B, Haynes BF, **Acharya P. Structural diversity of the SARS-CoV-2 Omicron spike.** *Molecular Cell*, Jun 2022, doi: 10.1016/j.molcel.2022.03.028.
 - Edwards RJ, Mansouri K, Stalls V, Manne K, Watts B, Parks R, Gobeil SMC, Janowska K, Li D, Lu X, Deyton M, Spreng J, Williams W, Saunders K, Sempowski GD, Henderson R, Alam M, Haynes BF, **Acharya P. Cold sensitivity of the SARS-CoV-2 spike ectodomain.** *Nat Struct Mol Biol*, Jan 2021 doi:10.1038/s41594-020-00547-5.
 - Gobeil S, Janowska K, McDowell S, Mansouri K, Parks R, Manne K, Stalls V, Kopp M, Henderson R, Edwards RJ, Haynes BF, **Acharya P. D614G mutation alters SARS-CoV-2 spike conformational dynamics and protease cleavage susceptibility at the S1/S2 junction.** *Cell Reports*, Dec 2020, doi: 10.1016/j.celrep.2020.108630
 - Henderson R, Edwards RJ, Mansouri K, Janowska K, Stalls V, Gobeil SMC, Kopp M, Li D, Parks R, Hsu AL, Borgnia MJ, Haynes BF, **Acharya P. Controlling the SARS-CoV-2 spike glycoprotein conformation.** *Nat Struct Mol Biol*, Oct 2020, 27(10):925-933, doi: 10.1038/s41594-020-0479-4. Epub 2020 Jul 22. PMID: 32699321

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