BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

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

As Director of the Division of Structural Biology, Duke Human Vaccine Initiative (DHVI), I lead the structural biology program at DHVI. My research group uses cryo-electron microscopy (cryo-EM) and x-ray crystallography for structural determination of HIV-1 Envelopes (Env) and SARS-CoV-2 spike, and their complexes with receptors and antibodies. Since moving to DHVI in July 2018, I have established a robust cryo-EM structural determination pipeline that has resulted in several atomic level structures of HIV-1 Env, and more recently, of SARS-CoV-2 spike complexes. The major focus of my research is to understand the structural details of conformational changes related to virus entry. A parallel direction is to visualize the interaction of viral surface proteins with host antibodies. Combining these two intersecting areas of basic research, my group interfaces with teams of virologists, immunologists and computational biologists, in a highly collaborative research environment at DHVI and beyond, to leverage our atomic level findings for vaccine development.

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

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. The goal of this proposal is to determine high-resolution structures of the initial site of CD4 engagement on the pre-fusion, closed HIV-1 Envelope (Env) trimer. We will also define the early, and yet unknown, CD4-induced conformational changes related to opening of the Env protomers, and movements of the HIV-1 fusion peptide.
Role: PI

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. The goal of this proposal is to determine high-resolution structures of the initial site of CD4 engagement on the pre-fusion, closed HIV-1 Envelope (Env) trimer. We will also define the early, and yet unknown, CD4-induced conformational changes related to opening of the Env protomers, and movements of the HIV-1 fusion peptide.
Role: PI

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. The goal of this proposal is to investigate the structure and dynamics of the conserved HIV-1 Env Phe43 cavity using CD4-mimetic miniprotein M48U1 as a molecular probe. We will determine structures of M48U1 bound to closed and open HIV-1 Env trimers. We will complement structural studies with cell-surface Env binding assays using a fluorescently labeled M48U1, and with neutralization assays. These studies will advance our understanding of the HIV-1 entry mechanism and the function and mechanics of a critical Env cavity.
Role: PI

UM1-AI144371 (PI: Haynes) 07/15/2019 – 06/30/2026
NIH
Induction of protective antibodies for HIV vaccine development
The overall goal of this grant is to develop an effective HIV-1 vaccine for global use.
Role: Investigator

Completed Research Support:

5UM1-AI100645 (PI: Haynes) 07/15/2012 - 06/30/2019
Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery
The overall goals of the CHAVI-ID research agenda have three foci: 1. Induction of Protective Antibody Responses, 2. Induction of Protective T Cell Responses and 3. Induction of Protective Innate Responses. Together, these goals constitute the path to overcoming the remaining obstacles preventing the development of an effective preventative HIV-1 vaccine.
Role: Investigator

UM1-AI068618 (PI: Acharya) 10/01/2018 – 09/30/2019
Fred Hutchinson CRC
Studying the effect on HIV-1 Env structure and immune response to HIV-1 infection in mucosal fluids using Negative Stain Electron Microscopy The goal of this proposal is to explore the effect that the mucosal environment has on the structure and antigenicity of HIV-1 Env proteins.
Role: PI

B. Positions and Honors

Positions and Employment

2003-2005 Visiting Scientist, Max Planck Institute of Biophysics, Frankfurt, and Max Planck Institute for Terrestrial Microbiology, Marburg, Germany
2005-2009 Visiting Fellow, Structural Biology Section (SBS), VRC, NIH, Bethesda, Maryland, USA
2009-2013 Research Fellow, SBS/VRC/NIAID/NIH, Bethesda, Maryland, USA
2013-2015 Research Scientist, SBS/VRC/NIAID/NIH Bethesda, Maryland, USA
2015-2018 Research Scientist, SEMC, NYSBC, New York, and SBS/VRC/ NIH, Bethesda, Maryland, USA
2018- present- Associate Professor, Department of Surgery, and Director of Structural Biology, DHVI, 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
2018 Translating Duke Health Initiative (TDHI) Scholar
2019 Outstanding Achievement Award, CHAVD, Duke Human Vaccine Institute, Duke University 2019
2020 Young Faculty Award, Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery
2021 Duke Presidential Award

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. I developed a high-throughput ELISA-based assay to discover 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. As part of a vaccine application of structural biology of HIV-1 entry, I co-led the VRC team that developed DS-SOSIP – an Env construct stabilized by disulfides designed to resist CD4-induced structural changes. DS-SOSIP is currently being manufactured at the VRC for use as an immunogen, and is widely used in the field for vaccine studies. I developed a CD4 triggering assay that was critical in identifying DS-SOSIP. Later, upon arrival at Duke, I collaborated with Drs. Alam and Haynes for cryo-EM structural determination of an Env immunogen that was designed to prevent CD4-induced triggering.
    a. Huang CC, Lam SN, **Acharya P**, Tang M, Xiang SH, Hussan SS, Stanfield RL, Robinson J, Sodroski J, Wilson IA, Wyatt R, Bewley CA, Kwong PD. **Structures of the CCR5 N terminus and of a tyrosine-sulfated antibody with HIV-1 gp120 and CD4.** *Science*, 317(5846):1930-1934, Sep 2007. PMCID: PMC2278242
    b. **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. PMCID: PMC2650494
    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*, 21(6):1018-1029, Jun 2013. PMCID: 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.* 2020 Jan 24;11(1):520. doi: 10.1038/s41467-019-14196-w. PMCID: PMC6981184

2. ***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.
    a. 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* 2021 Jun 24;eabi6226. doi: 10.1126/science.abi6226. Online ahead of print.
    b. 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,* 27(10):925-933, Oct 2020 doi: 10.1038/s41594-020-0479-4. Epub 2020 Jul 22. PMID: 32699321
    c. Edwards RJ, Mansouri K, Stalls V, Manne K, Watts B, Parks R, Gobeil SMC, Janowska K, Li D, Lu X, Deyton M, Sprenz 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.
    d. 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

3. ***Vaccine development targeting the HIV-1 Env CD4 binding site (CDbs).*** I determined the structure of the initial contact of CD4 with the HIV-1 Env, which defines the site that CD4bs-directed antibodies must target to effect HIV-1 neutralization. I led structural investigations into HIV-1 neutralizing antibodies derived from the VH1-46 heavy chain germline, and demonstrated a mode of binding distinct from the VRC01-class that derived from the VH1-2 germline. In more recent work done after I moved to DHVI in my new position 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.
    a. 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*, 24(4):370-378, Apr 2017. (§ Co-first author). PMCID: PMC5798227
    b. Zhou T, Zhu J, Wu X, Moquin S, Zhang B, **Acharya P**, Georgiev IS, Altae-Tran HR, Chuang GY, Joyce MG, Do Kwon Y, Longo NS, Louder MK, Luongo TS, McKee K, Schramm CA, Skinner J, Yang Y, Yang Z, Zhang Z, Zheng A, Bonsignori M, Haynes BF, Scheid JF, Nussenzweig MC, Simek M, Burton DR, Koff WC, NISC Comparative Sequencing Program, Mullikin JC, Connors M, Shapiro L, Nabel GJ, Mascola JR, Kwong PD. **Multidonor Analysis Reveals Structural Elements, Genetic Determinants, and Maturation Pathway for HIV-1 Neutralization by VRC01-Class Antibodies.** *Immunity*, 39(2):245-258, Aug 2013. PMCID: PMC3985390
    c. Zhou T§, Lynch RM§, Chen L§, **Acharya P**§, Wu X, Doria-Rose NA, Joyce MG, Lingwood D, Soto C, Bailer RT, Ernandes MJ, Kong R, Longo NS, Louder MK, McKee K, O'Dell S, Schmidt SD, Tran L, Yang Z, Druz A, Luongo TS, Moquin S, Srivatsan S, Yang Y, Zhang B, Zheng A, Pancera M, Kirys T, Georgiev IS, Gindin T, Peng HP, Yang AS; NISC Comparative Sequencing Program, Mullikin JC, Gray MD, Stamatatos L, Burton DR, Koff WC, Cohen MS, Haynes BF, Casazza JP, Connors M, Corti D, Lanzavecchia A, Sattentau QJ, Weiss RA, West AP Jr, Bjorkman PJ, Scheid JF, Nussenzweig MC, Shapiro L, Mascola JR, Kwong PD. **Structural Repertoire of HIV-1-Neutralizing Antibodies Targeting the CD4 Supersite in 14 Donors.** *Cell*, 161(6):1280-1292, May 2015. (§ Co-first author). PMCID: PMC4683157
    d. 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. (2019) Plos Pathog. 15(9):e1008026. doi: 10.1371/journal.ppat.1008026. [Epub ahead of print].

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. In a subsequent collaboration with Dr. Marzena Pazgier, I solved 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*, 88(21):12895-12906, Aug 2014. PMCID: 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 Structures of Antibody N60-i3 and Antibody JR4 in Complex with gp120 Define More Cluster A Epitopes Involved in Effective Antibody-Dependent Effector Function against HIV-1.** *J Virol*, 89(17):8840-8854, Jun 2015. PMCID: PMC4524080

5. ***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. Here I solved the structures of 8 fusion peptide-directed antibodies, at resolutions ranging from 3.6-4.4 Å, by cryo-EM. These

structure-function studies revealed distinct modes of antibody recognition of the fusion peptide.

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*, 352(6287):828-833, May 2016. PMCID: 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, 14(7):e1007159, Jul 2018. (§ 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*, 178(3):567-584, July 2019 (§ Co-first author)

Complete Listing of Published Work: https://tinyurl.com/usskmux