

**BIOGRAPHICAL SKETCH**

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NAME: Eva Harris

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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
Harvard University, Cambridge, MA	B.A., mcl	06/1987	Biochemical Sciences
University of California, Berkeley, CA	Ph.D.	05/1993	Molecular & Cell Biology
University of California, San Francisco, CA	Post-doc	05/1996	Molecular Pathogenesis

**PERSONAL STATEMENT:**

I am a Professor in the Division of Infectious Diseases and Vaccinology in the School of Public Health, Director of the Center for Global Public Health, and Chair of the Infectious Diseases and Immunity Graduate Group at the University of California, Berkeley. I have developed a multidisciplinary approach to study the molecular virology, pathogenesis, immunology, clinical aspects, epidemiology, and control of dengue, Zika and chikungunya, the most prevalent arboviral diseases in humans. My work addresses viral and host factors that modulate disease severity and investigates immune correlates of protection and pathogenesis using *in vitro* approaches, animal models, and research involving human populations. One major focus is on studies of arboviral disease in humans, including antibody and B cell responses and correlates of protection, systems immunology profiling of the innate response, diagnostics and seroprevalence studies, and viral evolution, fitness, and intrahost diversity. Another focus is viral pathogenesis, specifically the role of the flavivirus NS1 protein in endothelial permeability, vascular leak, and viral dissemination. My international work focuses on laboratory-based and epidemiological studies of dengue, chikungunya, Zika, and influenza in Latin American countries, particularly in Nicaragua, where ongoing projects include clinical and biological studies of severe disease, a pediatric cohort study of dengue, chikungunya, Zika and influenza transmission in Managua, and a recently concluded cluster randomized controlled trial of evidence-based, community-derived interventions for prevention of dengue via control of its mosquito vector. *This work has led to over 310 peer-reviewed publications.* I have been PI on >45 grants, including 8 R series awards, a U19 (HIPC), a Program Project (P01), and a U01 (Centers for Research in Emerging Infectious Diseases) from NIH. In 1997, I received a MacArthur "Genius" Award for my pioneering work over the previous ten years developing programs and working to build scientific capacity in developing countries to address public health and infectious disease issues. To continue and expand this work, in 1998 I founded a non-profit organization Sustainable Sciences Institute with offices in San Francisco and Nicaragua and published a book on the subject with Oxford University Press. In 2001, I was named a Pew Scholar for my work on dengue pathogenesis. In 2002, I received a national recognition award from the Minister of Health of Nicaragua for my contribution to scientific development and was selected as a "Global Leader for Tomorrow" by the World Economic Forum. In 2012, I received a Global Citizen Award from the United Nations Association. In 2012, I was elected Councilor and in 2018 appointed Fellow of the American Society of Tropical Medicine and Hygiene, and in 2019, I received the Beijerinck Virology Prize from the Royal Netherlands Society of Arts and Sciences. I currently serve on the Scientific Council of the Institut Pasteur, the Advisory Board of the Pew Latin American Fellows Program, the Forum on Microbial Threats of the National Academy of Sciences, and the Lancet Commission on *Aedes*-borne viral diseases.

## RESEARCH AND PROFESSIONAL EXPERIENCE:

1993-2001 Director, Applied Molecular Biology/Appropriate Technology Transfer Program, UCSF/UCB  
1997-1999 Assistant Adjunct Professor, Program in Molecular Pathogenesis, UC San Francisco, CA  
1998-present President, Sustainable Sciences Institute, San Francisco, CA  
1998-2005 Assistant Professor, Division of Infectious Diseases, School of Public Health, UC Berkeley, CA  
2005-2008 Associate Professor, Division of Infectious Diseases, School of Public Health, UC Berkeley  
2007-2008 Associate Dean for Research, School of Public Health, UC Berkeley  
2008-present Professor, Division of Infectious Diseases, School of Public Health, UC Berkeley  
2007-present Director, Center for Global Public Health, School of Public Health, UC Berkeley  
2016-present Chair, Infectious Diseases and Immunity Graduate Group (PhD program), SPH, UC Berkeley

## HONORS AND AFFILIATIONS:

1988-1991 National Science Foundation Graduate Fellowship  
1991-1993 Berkeley Graduate Fellowship, University of California, Berkeley  
1997 *Doctor Honoris Causa*, Universidad Mayor de San Andrés, La Paz, Bolivia  
1998-present Visiting Professor, Universidad Autónoma de Guerrero, Acapulco, México  
1997-2002 MacArthur Fellowship, John D. and Catherine T. MacArthur Foundation  
1998-2001 King Sweesy and Robert Womack Chair in Medical Research and Public Health, UC Berkeley  
2001-2005 Pew Scholar, Pew Scholars Program in the Biomedical Sciences, Pew Charitable Trusts  
2002 Prytanean Alumnae Faculty Award, UC Berkeley Prytanean Faculty Association  
2002 Global Leader for Tomorrow, World Economic Forum  
2002 Award from Minister of Health, Nicaragua, recognizing support of scientific development  
2012 Global Citizen Award, United Nations Association, East Bay Chapter  
2018 Fellow, American Society of Tropical Medicine and Hygiene  
2019 Beijerinck Virology Prize, Royal Netherlands Society of Arts and Sciences

## PROFESSIONAL ACTIVITIES

1995 Invited Participant, IOM/NRC Meeting on Emerging Infectious Diseases, NAS  
1999, 2002 Reviewer, NIH Study Section for NIAID "Int'l Collaborations in Infectious Disease Research"  
1999-2005 Member, US National Committee for the IUBMB, National Academy of Sciences  
1999-present Reviewer, *J Virol*, *J Infect Dis*, *J Immunol*, *Am J Trop Med Hyg*, *EID*, *Clin Infect Dis*, *Science*, *J Gen Virol*, *Virology*, *PLoS Med*, *PLoS Negl Trop Dis*, *PLoS Path*, *Nat Med*, *Nat Comm*  
2000,2,5,7,9 Temporary Advisor, World Health Organization and Pan American Health Organization  
2000 Reviewer, NIH Study Section for NIAID "Tropical Medicine Research Centers"  
2001 International Organizing Committee, WHO Conference "Harnessing Biotechnology for Health"  
2001 Frontiers of Science Symposium, National Academy of Sciences (Speaker)  
2002-2003 Consultant, Health Equity, Rockefeller Foundation  
2004 International Organizing Committee, WHO World Summit on Health Research  
2004 Reviewer, Ellison Medical Foundation, Global Infectious Diseases Program  
2005-present Advisory Committee, President's Postdoctoral Fellowship Program, UC Office of the President  
2006 Reviewer, Virology A Study Section, NIAID, NIH  
2006-8 Program Committee, American Society for Virology  
2007-2011 Reviewer and Chair, ICP1 Study Section, NIH; Chair (2009), ICP2-B Study Section, NIH  
2007-present Associate Editor, *PLoS Neglected Tropical Diseases*  
2009 Invited Plenary, American Society for Virology Annual Meeting  
2010 Howard Hughes Medical Institute Holiday Lecture  
2011 Invited Speaker, NIH Wednesday Aftnoon Lecture Series  
2012 Editor/Reviewer, Transformative R01 Study Section, NIH  
2012-present Chair, Scientific Organizing Committee, Pan American Dengue Research Network Meeting  
2012-2014 Scientific Advisory Board, Novartis Institute of Tropical Diseases  
2012-2016 Council, American Society of Tropical Medicine and Hygiene  
2013-2016 Steering Committee, Models of Infectious Disease Agent Study (MIDAS), NIH  
2013-2016 Standing Member, Clinical Research and Field Studies (CRFS) Study Section, NIH  
2014-2016 Participant, Scientific Advisory Board during Phase 3 Dengue Vaccine Trials, Sanofi Pasteur  
2014 Member (Ad hoc), NIAID Council, NIH  
2014-2017 Member, Scientific Advisory Board, SMART Infectious Diseases Program  
2015-2016 Executive Committee/lead organizer, PDC Mtg on Dengue Immune Correlates of Protection

2016	Member, World Health Organization Expert Panel on the Zika Causality Framework
2016-present	Member, Scientific Council, Institut Pasteur
2017-present	National Academy of Sciences, Engineering, and Medicine Forum on Microbial Threats
2018-present	Advisory Board, Pew Latin American Fellows Program
2019-present	Lancet Commission, Urban Mosquito-borne Viral Diseases

## CONTRIBUTIONS TO SCIENCE

### 1. Flavivirus NS1 protein triggers endothelial permeability and vascular leak.

A major contribution to the understanding of flavivirus pathogenesis is our discovery that the DENV nonstructural protein 1 (NS1) protein induces both permeability in human endothelial cell monolayers and vascular leak *in vivo*, which can be prevented by polyclonal and monoclonal antibodies and vaccination with recombinant NS1. This was an important breakthrough given that the most severe forms of dengue disease are associated with increased vascular leakage that result in hypotension, shock and potentially death. We then dissected the mechanisms responsible, identifying endothelial cell-intrinsic pathways of NS1-triggered disruption of the integrity of the endothelial glycocalyx layer via activation of sialidases and the cathepsin L/heparanase pathway, leading to shedding of sialic acid and heparan sulfate moieties from the cell surface. Activation of these pathways requires clathrin-mediated endocytosis of NS1. We showed that this mechanism is distinct both *in vitro* and *in vivo* from the NS1-mediated release of inflammatory cytokines that could also contribute to vascular leak. We have also found that NS1 increases endothelial hyperpermeability *in vitro* via dysregulation of intercellular junction proteins. In an exciting extension of this work that encompasses NS1 proteins from other flaviviruses, we demonstrated that NS1 proteins from dengue, Zika (ZIKV), West Nile (WNV), Japanese encephalitis (JEV), and yellow fever (YFV) viruses selectively bind to and alter the permeability of human endothelial cell monolayers from lung, dermis, umbilical vein, brain, and liver *in vitro* and cause vascular leakage upon inoculation into mice in a tissue-dependent manner, reflecting the pathophysiology of each flavivirus. Recent evidence also indicates that these different flavivirus NS1 proteins may modulate virus dissemination into particular tissues, leading to pathogenesis and disease. We are now identifying the molecular determinants on NS1 and host proteins responsible for these pathogenic processes. Recently, we have extended similar studies to SARS-CoV-2, demonstrating that the Spike protein alone can also cause endothelial permeability and identifying the mechanism. These studies have led to ~15 publications thus far.

- a. Beatty, P.R., Guardo, H.P., Killingbeck, S., Glasner, D., Hopkins, K., and **Harris, E.** (2015) Dengue virus non-structural protein 1 (NS1) triggers vascular leak that can be inhibited by anti-NS1 antibodies. *Sci Transl Med* 7:304ra141.
- b. Puerta-Guardo, H., Glasner, D.R., and **Harris, E.** (2016) Dengue virus NS1 disrupts the endothelial glycocalyx, leading to hyperpermeability. *PLoS Pathog.* 12(7):e1005738. PMC4944995
- c. Wang, C., Puerta-Guardo, H., Biering, S.B., Glasner, D.R., Tran, E.B., Patana, M., Gomberg, T.A., Malvar, C., Espinosa, D.A., and **Harris, E.** (2019) Endocytosis of flavivirus NS1 is required for NS1-mediated endothelial hyperpermeability and is abolished by a single N-glycosylation site mutation. *PLoS Pathog.* 15(7):e1007938
- d. Puerta-Guardo, H., Glasner, D.R., Espinosa, D.A., Biering, S.B., Patana, M., Ratnasiri, K., Wang, C., Beatty, P.R., and **Harris, E.** (2019) Flavivirus NS1 triggers tissue-specific vascular endothelial dysfunction reflecting disease tropism. *Cell Rep.* 26(6):1598-1613.e8. PMC6934012
- e. Biering, S.B., Akey, D., Wong, M.P., Brown, W.C., Lo, N.T.N., Puerta-Guardo, H., Tramontini Gomes de Sousa, F., Wang, C., Konwerski, J.R., Espinosa, D.A., Bockhaus, N.J., Glasner, D.R., Li, J., Blanc, S.F., Juan, E.Y., Elledge, S.J., Mina, M.J., Beatty, P.R., Smith, J.L., **Harris, E.** (2021) Structural basis for antibody-mediated inhibition of dengue virus NS1-triggered endothelial dysfunction and vascular leak. *Science.* 371:194–200.

### 2. Dengue virus translation/replication and host-virus interactions.

My laboratory performed a series of investigations to define viral and host determinants that modulate DENV translation and replication. This led to the discovery of a non-canonical mechanism of DENV translation that could provide a survival advantage under certain infection conditions and to the identification of novel *cis* sequence and structural elements that control viral RNA translation and replication. We also further defined the molecular requirements for 5'-3' circularization of the viral genome for both translation and replication of the DENV RNA and identified *trans* cellular factors involved in regulation of these processes. Finally, we characterized the host response to DENV infection in relation to modulation of the unfolded protein response

and the rearrangement and expansion of the endoplasmic reticulum. We have recently extended work on host virus interactions and viral pathogenesis to Zika virus. This work comprises ~30 publications.

- a. Edgil, D., Polacek, C., and **Harris, E.** (2006) Dengue virus utilizes a novel strategy for translation initiation when cap-dependent translation is inhibited. *J. Virol.* 80:2976-2986. PMC1395423
- b. Paranjape, S. and **Harris, E.** (2007) Y box-binding protein-1 binds to the dengue virus 3' untranslated region and mediates anti-viral effects. *J. Biol. Chem.* 282:30497-30508.
- c. Peña, J. and **Harris, E.** (2011) Dengue virus modulates the unfolded protein response in a time-dependent manner. *J. Biol. Chem.* 286:14226–14236. PMC3077624
- d. Tabata, T., Petitt, M., Puerta-Guardo, H., Michlmayr, D., Wang, C., Fang-Hoover, J., **Harris, E.\*** and Pereira, L. (2016) Zika virus targets different primary human placental cells, suggesting two routes for vertical transmission. *Cell Host Microbe*, 20(2):155-66. \*Co-corresponding authors PMC527282

### 3. Investigation of the human immune response to DENV and ZIKV infection

A long-standing interest of my group is to leverage our 33-year collaboration with Nicaraguan colleagues to investigate the human immune response to DENV and ZIKV infection and to identify correlates of protection and pathogenesis. To do so, we analyze the well-characterized serum and peripheral blood mononuclear cell (PBMC) samples from our two on-going long-term prospective studies in Managua, Nicaragua -- the community-based pediatric cohort study (now in its 18<sup>th</sup> year) and the hospital-based study of pediatric arboviral diseases (now in its 23<sup>rd</sup> year). The focus in my laboratory is on the B cell and antibody response, with on-going collaborations to address gene expression profiling, immune cell phenotyping and T cell responses. Important findings, selected from ~35 publications, have included analysis of the cross-reactive DENV-specific B cell response, and convergent immune signatures in multiple dengue patients associated with specific CDR3 sequences. We established that anti-DENV neutralizing antibody titers correlate with reduced probability of symptomatic DENV infection in our cohort study and thus can serve as a correlate of protection. Conversely, we have shown that specific antibody titers (post-DENV and post-ZIKV infection) are predictive of severe disease, confirming antibody-dependent enhancement of dengue disease severity in human populations for the first time and establishing a potential correlate of risk. Both these findings have important implications for studies of natural infections and vaccine trials. I direct an NIH P01 program grant and co-direct a HIPC U19 to investigate innate and adaptive immune correlates of protection in natural infections and vaccines to expand this work. Since 2016, we also extended our work on both pathogenesis and immunology to Zika.

- a. Katzelnick, L. Montoya, M, Gresh, L, Balmaseda, A., and **Harris, E.** (2016) Neutralizing antibody titers against dengue virus correlate with protection from symptomatic infection in a longitudinal cohort. *Proc Natl Acad Sci USA*, 113(3):728-33. PMC4725482
- b. Michlmayr D, Andrade P, Gonzalez K, Balmaseda A, **Harris E.** (2017) CD14<sup>+</sup> CD16<sup>+</sup> monocytes are the main targets of Zika virus infection in peripheral blood mononuclear cells in a paediatric study in Nicaragua. *Nat Microbiol.* 2(11):1462-1470.
- c. Katzelnick., L. Gresh, L, Halloran, M.E., Mercado, J.C., Kuan, G., Gordon, A., Balmaseda, A., and **Harris, E.** (2017) Antibody-dependent enhancement of severe dengue disease in humans. *Science.* 358:929-32.
- d. Andrade, P., Gimblet-Ochieng, C., Modirian, F., Collins, M., Cárdenas, M., Katzelnick, L., Montoya, M., Michlmayr, D., Kuan, G., Balmaseda, A., Coloma, J., de Silva, A., **Harris, E.** (2019) Impact of pre-existing dengue immunity on human antibody and memory B cell responses to Zika. *Nat. Commun.* 10(1):938.
- e. Katzelnick, L.C., Narvaez, C., Arguello, S., Lopez Mercado, B., Collado, D., Ampie, O., Elizondo, D., Miranda, T., Bustos Carillo, F., Mercado, J.C., Latta, K., Schiller, A., Segovia-Chumbez, B., Ojeda, S., Sanchez, N., Plazaola, M., Coloma, J., Halloran, M.E., Premkumar, L., Gordon, A., Narvaez, F., De Silva, A.M., Kuan, G., Balmaseda, A., **Harris, E.** (2020) Zika virus infection enhances future risk of severe dengue disease. *Science.* 369:1123-1128.

### 4. Characterization of anti-DENV and anti-ZIKV polyclonal and monoclonal antibodies

Through collaborative studies and >20 publications, we have defined the characteristics of human polyclonal and monoclonal antibodies (MAbs) against DENV and ZIKV, using our mouse models of protection and enhancement to complement *in vitro* assays. We demonstrated that MAbs act therapeutically *in vivo* by being both highly neutralizing *and* suppressing the enhancing potential of pre-existing antibodies. We contributed to generation of human MAbs (from children in our Nicaraguan studies) and characterization of the protective efficacy as well as enhancing ability of MAbs *in vivo*. We also analyzed antibody subsets in human polyclonal

DENV-immune sera and showed that removal of serotype cross-reactive antibodies ablated enhancement of heterotypic virus infection *in vitro* and antibody-enhanced mortality *in vivo*. These studies blending *in vitro* and *in vivo* studies have shed light on the properties and mechanisms of antibodies that lead to neutralization/protection versus enhancement of DENV and ZIKV infection.

- a. de Alwis, R., Williams, K.L. Schmid, M.A., Patel, B., Lai, C.-Y., Smith, S.A., Crowe, J.E., Wang<sup>3</sup>, W.-K., **Harris, E.\***, de Silva, A.M.\* (2014) Dengue viruses are enhanced by distinct populations of serotype cross-reactive antibodies in human immune sera. *PLoS Pathog.* 10(10):e1004386. \*co-corresponding authors PMC4183589
- b. Stettler, K., Beltramello, M., Espinosa, D...**Harris, E.**, Lanzavecchia, A., Sallusto, F., & Corti, D. (2016) Specificity, cross-reactivity and function of antibodies elicited by Zika virus infection. *Science.* 353(6301):823-6.
- c. Andrade, D.V., Katzelnick, L.C., Widman, D.G., Balmaseda, A., de Silva A.M., Baric, R.,S., and **Harris, E.** (2017) Analysis of individuals from a dengue-endemic region helps define the footprint and repertoire of antibodies targeting dengue virus 3 type-specific epitopes. *mBio.* 8(5):e01205-17. PMC5605938
- d. Montoya, M., Collins, M., Balmaseda, A., Srean, G., de Silva, A.M., **Harris, E.** (2018) Longitudinal analysis of antibody cross-neutralization following Zika and dengue virus infection in Asia and the Americas. *J. Infect. Dis.* 218(4):536-545.
- e. Young, E., Carnahan, R.H., Andrade, D.V., Kose, N., Nargi, R.S., Doyle, M.P., Fritch, E.J., Munt, J., White, L., Baric, T.J., Stoops, M., DeSilva, A., Tse, L.V., Martinez<sup>1</sup>, D.R., Zhu, D., Metz, S., Wong, M.P., Espinosa, D.A., Montoya, M., Biering, S.B., Sukulpolvi-Petty, S., Kuan, G., Balmaseda, A., Diamond, M.S., **Harris, E.\***, Crowe, J.E.Jr.,\* Baric, R.S.\* (2020) Identification of six new dengue virus serotype 3 specific human neutralizing antigenic sites. *Cell Host Microbe.* 27(5):710-724.e7 \*Co-corresponding authors

## 5. Development and use of mouse models of DENV infection, disease, and immune response

Another major research area (~25 publications) has been the generation of a mouse model of DENV infection and disease that we use for mechanistic studies of dengue pathogenesis and immune response, which we then correlate with human DENV infection, disease, and immune responses in our studies in Nicaragua (see below). These parallel studies have focused on virus tropism, immune response, and viral structure/function. Major findings have included the first *in vivo* demonstration of lethal antibody-dependent enhancement of DENV infection, characterization of waves of DENV infection of immune cells in an intradermal model of infection, and the discovery of a direct role for DENV NS1 protein alone in inducing vascular leak *in vivo*. We have also established a mouse model of Zika for use in investigating pathogenesis, evaluating vaccines and studying monoclonal and polyclonal anti-ZIKV antibodies.

- a. Shresta, S., Sharar, K.L., Prigozhin, D.M., Beatty, P.R., and **Harris, E.** (2006) Murine model for dengue lethal disease with increased vascular permeability. *J. Virol.* 80: 10208-10217. PMC1617308
- b. Balsitis, S.\*, Williams, K.L.\*, Lachica, R., Flores, D., Kyle, J.L., Mehlhop, E., Johnson, S., Diamond, M., Beatty, P.R., and **Harris, E.** (2010) Lethal antibody enhancement of dengue disease in mice is prevented by Fc modification. *PLoS Path.* 6 :e1000790. PMC2820409
- c. Schmid, M.A. and **Harris, E.** (2014) Monocyte recruitment to the dermis and differentiation to dendritic cells increases the targets for dengue virus replication. *PLoS Pathog.* 10(12):e1004541. PMC4256458
- d. Schmid, M.A., Glasner, D.R., and **Harris, E.** (2016) Mosquito saliva increases endothelial permeability in the skin, immune cell migration, and dengue pathogenesis during antibody-dependent enhancement. *PLoS Pathog.* 12(6):e1005676. PMC4911004
- e. Wang J, Bardelli M, Espinosa DA...**Harris E**, Lok SM, Varani L, Corti D. (2017) A human bi-specific antibody against Zika virus with high therapeutic potential. *Cell.* 171(1):229-241.

## 6. Dengue virus evolution and fitness; chikungunya and Zika virus sequencing

A series of studies (~15 publications) have addressed DENV evolution and fitness, stemming from sequence and phylogenetic analysis of the circulating serotypes, genotypes and clades in our studies in Nicaragua. Importantly, we have combined these with functional studies of the viruses in question. In one large study of DENV2 clade replacement temporally associated with an increase in disease severity, we found it was the complex interaction of viral genetics and population dynamics of serotype-specific immunity that *together* contributed to risk of severe dengue disease. We also showed via *in vitro* analyses of viral isolates from the different clades (NI-1 vs. NI-2B) and analysis of patient viremia a more fit virus likely emerged in later epidemic seasons. We then analyzed the replicative ability of the two clades in mosquito cell lines and *Ae. aegypti* mosquitoes reared from eggs collected in Managua and showed that clade NI-2B holds a replicative advantage

early in infection. We have extended full-length sequencing studies to chikungunya and Zika in Nicaragua. Another focus has been investigating intrahost diversity in samples from our Nicaraguan studies.

- a. OhAinle, M., Balmaseda, A., Macalalad, A.R., Tellez, Y., Zody, M.C., Saborío, S., Nuñez, A., Lennon, N.J., Birren, B.W., Gordon, A., Henn, M.R., **Harris, E.** (2011) Dynamics of dengue disease severity determined by the interplay between viral genetics and serotype-specific immunity. *Science Transl Med.* 3:114ra128.
- b. Parameswaran, P., Charlebois, P., Tellez, Y., Nunez, A., Ryan, E.M., Malboeuf, C.M., Levin, J.Z., Lennon, N., Balmaseda, A., **Harris, E.\***, and Henn, M.R.\* (2012) Genome-wide patterns of intrahuman dengue virus diversity reveal associations with phylogenetic clade and interhost diversity. *J. Virol.* 86(16):8546. PMC3421746 \*Co-corresponding authors.
- c. Quiner, C.A., Parameswaran, P., Ciota, A.T., Ehrbar, D.J., Dodson, B.L., Schlesinger, S., Kramer, L.D., and **Harris, E.** (2014) Increased replicative fitness of a dengue virus 2 clade in native mosquitoes: Potential contribution to a clade replacement event in Nicaragua. *J. Virol.* 88(22):13125-34. PMC4249086
- d. Manokaran, G., Finol, E., Wang, C., Gunaratne, J., Bahl, J., Ong, E.Z., Tan<sup>2</sup>, H.C., Sessions, O.M., Ward, A.M., Gubler, D.J., **Harris, E.**, Garcia-Blanco, M.A., and Ooi, E.E.. (2015) Subgenomic RNA of dengue-2 virus binds tripartite motif 25 protein to inhibit interferon expression providing a mechanism for epidemiological fitness. *Science.* 350(6257):217-21.
- e. Parameswaran, P., Wang, C., Trivedi, S.B., Eswarappa, M., Montoya, M., Balmaseda, A., and **Harris, E.** (2017) Intrahost selection pressures drive rapid dengue virus microevolution in acute human infections. *Cell Host Microbe.* 22(3):400-410.e5.

## 7. Epidemiology of dengue, chikungunya, Zika, and influenza

I have been active over the last 24 years in directing studies on the epidemiology of dengue and more recently chikungunya, Zika, and influenza in Nicaragua, based on our 21-year hospital-based study, our 21-year cohort study, and other studies in communities, health centers and hospitals in Nicaragua. These studies have led to ~60 papers, documenting trends in transmission, the effect of viral genetics, prior host immunity, and interval between infections on the outcome of infection, the expansion factor needed to calculate the true burden of disease, and a cluster-randomized controlled trial to show the effectiveness of evidenced-based community participation in mosquito control for the prevention of dengue, among others. In 2014, we initiated a series of similar projects on chikungunya, including studies of incidence, clinical attack rate, seroprevalence, phylogenetics, etc. and in 2016 initiated an expanded series of studies on Zika, including three studies of Zika in pregnant women in Nicaragua.

- a. Montoya, M.,\* Gresh, L.,\* Mercado, J.C., Williams, K.L., Vargas, M.J., Gutierrez, G., Kuan, G., Gordon, A., Balmaseda, A., **Harris, E.** (2013) Symptomatic versus inapparent outcome in repeat dengue virus infections is influenced by the time interval between infections and study year. *PLoS Negl Trop Dis.* 7:e2357.
- b. Andersson, N., Nava-Aguilera, E., Arostegui, J., Morales-Perez, A., Suazo-Laguna, H., Legorreta-Soberanis, J., Hernandez-Alvarez, C., Fernandez-Salas, I., Balmaseda, A., Cortés-Guzmán, A.J., Coloma, J., Ledogar, R.J., and **Harris, E.** (2015) Camino Verde (Green Way) to Dengue Prevention: a pragmatic cluster-randomised controlled trial of evidence-based community mobilisation in Nicaragua and Mexico. *BMJ* 351:h3267.
- c. Burger-Calderon, R., Gonzalez, K., Ojeda, S., Zambrana, J.V., Sanchez, N., Cerpas Cruz, C., Suazo Laguna, H., Bustos, F., Plazaola, M., Lopez Mercado, B., Elizondo, D., Arguello, S., Carey Monterrey, J., Nuñez, A., Coloma, J., Waggoner, J.J., Gordon, A., Kuan, G., Balmaseda, A., **Harris, E.** Zika virus infection in Nicaraguan households. *PLoS Negl. Inf. Dis.* 12(5):e0006518. PMID: 29851968.
- d. Zambrana, J.V., Bustos, F., Burger-Calderon, R., Collado, D., Jairo, Sanchez, N., Ojeda, S., Plazaola, M., Lopez, B., Arguello, S., Elizondo, D., Aviles, W., Kuan, G., Balmaseda, A., Gordon, A., **Harris, E.** (2018) Seroprevalence, risk factor, and spatial analysis of Zika virus infection after the 2016 epidemic in Managua, Nicaragua. *Proc. Natl. Acad. Sci. USA.* 115(37):9294-9299. PMC6140532
- e. Gordon, A., Gresh, L., Ojeda, S., Katzelnick, L., Sanchez, N., Mercado, J., Chowell, G., Lopez, B., Elizondo, D., Coloma, J., Burger-Calderon, R., Kuan, G., Balmaseda, A., **Harris, E.** (2019) Prior dengue virus infection protects against Zika in a pediatric cohort in Nicaragua. *PLoS Med.* 16(1): e1002726.

## 8. Clinical research and laboratory diagnostics

Another area of research, resulting in >60 papers, is clinical research and the development and application of diagnostic assays for dengue, Zika, chikungunya and other infectious diseases. This includes work on the classification of dengue severity, which led to the inclusion of Nicaragua in the multi-center WHO/TDR study that formed the basis for the new dengue guidelines; validation and implementation of ultrasound as a

prognostic indicator of vascular leak; development of new serological and molecular biological assays for diagnosis and typing of dengue, chikungunya, and Zika; characterization of clinical features and biomarkers of DENV infection and disease, and the like. Our assay to distinguish anti-ZIKV from anti-DENV antibodies with high sensitivity and specificity has been important in the field and has led to many useful applications.

- a. Balmaseda, A., Hammond, S.N., Perez, L., Tellez, Y., Saborío, S.I., Mercado, J.C., Perez, M.A., Silva, S., Rocha, C., and **Harris, E.** (2006) Serotype-specific differences in clinical manifestations of dengue. *Am. J. Trop. Med. Hyg.* 74:449-456.
- b. Narvaez, F.,\* Gutierrez, G.\*, Perez, M.A., Elizondo, D., Nuñez, A., Balmaseda, A., and **Harris, E.** (2011) Evaluation of the traditional and revised WHO classifications of dengue disease severity. *PLoS Negl Trop Dis.* 5:e1397. PMC3210746
- c. Waggoner JJ, Gresh L, Mohamed-Hadley A, Ballesteros G, Vargas Davila MJ, Tellez Y, Sahoo, M.K., Balmaseda, A., **Harris, E.**, and Pinsky, B.A. (2016) Single-reaction multiplex PCR for detection of Zika, chikungunya, and dengue viruses. *Emerg Infect Dis.* Jul 15;22(7):1295-7.
- d. Balmaseda, A., Stettler, K., Carrera, R.M., Collado, D., ... **Harris, E.**#, Corti, D.# (2017) A novel antibody-based assay discriminates Zika virus infection from other flaviviruses. *Proc. Natl. Acad. Sci. USA* 14(31):8384-8389. #Co-corresponding authors. PMC5547631
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## 9. Scientific Capacity Building

Since 1988, I have developed programs and worked to build scientific capacity in developing countries to address public health and infectious disease issues. To continue and expand this work, in 1998, I founded a non-profit organization, Sustainable Sciences Institute, with offices in San Francisco, Managua, Nicaragua, and Cairo, Egypt. Over 20 publications on this topic, including a number of invited reviews and book chapters, have focused on methodology, process, health equity, and advocacy for strengthening scientific capability across the board (laboratory, epidemiology, manuscript-writing grant-writing, ethical issues, bio-informatics) especially in “scientifically-lagging” countries and working to bridge the scientific divide.

- a. **Harris, E.** (1996) Developing essential scientific capability in countries with limited resources. *Nat. Med.*, 2:737-739.
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- c. Coloma, J. and **Harris, E.** (2009) From construction workers to architects: Developing scientific research capacity in low-income countries. *PLoS Biol.* 7:e1000156.
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Complete List of Published Work in MyBibliography: <http://www.ncbi.nlm.nih.gov/sites/myncbi/12Sg-8tp-CpQN/bibliography/40921741/public/?sort=date&direction=ascending>.

## D. Research Support (Selected active on-going grants)

P01 AI106695 (Harris Program Director, PI Project 1, Core C)      NIAID/NIH  
7/1/15-6/30/25

### Protective immunity following dengue virus natural infections and vaccination

The main goal of this Program Project is to bring together a consortium of leading experts in B and T cell immunology together with our studies in Nicaragua and vaccine developers to improve understanding of the human B and T cell response to DENV natural infection and vaccination and identify adaptive immune correlates of protection from disease.

R01AI153416 (Harris PI)      NIAID/NIH  
8/1/21-7/31/26

### Living in the post-Zika world: Impact of interactions between dengue and Zika viruses on diagnostics, antibody dynamics, and correlates of protection and risk

The goal of this grant is to deploy new assays and modeling approaches to study how DENV and ZIKV cross-reactivity affects diagnostic testing, seroprevalence, viral transmission, and protection and/or

enhancement of future flaviviral disease in the context of the longest running dengue/Zika cohort study in Nicaragua.

R01 AI124493 (Harris PI)

NIAID/NIH 2/15/16-1/31/21 (NCE to 1/31/22)

**Determining novel mechanisms of dengue virus NS1-induced vascular leak**

The main goal of this project is to use our *in vitro* and *in vivo* models of dengue virus vascular leak to define the novel contributions of secreted DENV NS1 protein to dengue pathogenesis, advancing a critical new area of research, improving our understanding of severe dengue disease, and opening new pathways for treatment.

U19 AI118610 (Harris Co-Program Director; PI Project 1, Chik, Zika, ZIP Suppl) NIAID/NIH 7/1/15-6/30/22

**Dengue Human Immunology Project Consortium (DHIPC); Project 1 Immune profiling of natural dengue virus infections; Chikungunya and Zika supplements**

The main goal of this program is to develop molecular signatures that define immune response of dengue virus infection and vaccination. We will use “omics” technology platforms including immune profiling, genomics, RNAi, and proteomics to study well-characterized human cohorts of DENV-infected children (Project 1), chikungunya patients, Zika cases, dengue vaccines (Project 2), and infection of human cells from healthy donors (Project 3).

U01 AI151788 (Harris MPI)

NIAID/NIH

7/20/20-5/31/25

**CREID: Asian and American Center for Arbovirus Research and Enhanced Surveillance (A2CARES)**

This A2CARES Center for Research in Emerging Infectious Disease (CREID) includes a consortium of partners in Nicaragua, Ecuador, Sri Lanka and the US and has an overarching goal of developing an interconnected, harmonized network of clinical and laboratory sites to provide the foundation for research programs, compare arboviral diseases across geographic regions, develop and implement cutting-edge molecular and serological testing methods, and respond efficiently and effectively to new disease outbreaks.

R21 AI146464 (Harris PI)

NIAID/NIH

4/1/20-3/31/22

**Mechanism and *in vivo* activity of novel glycan-based therapy against flavivirus endothelial permeability and vascular leak**

This study proposes to evaluate selected glycan-based compounds for the ability to inhibit dengue and Zika virus infection as well as viral nonstructural protein 1 (NS1)-induced endothelial hyperpermeability and to determine their mechanism of action *in vitro* and *in vivo* in mouse models

R21 AI146464 (Harris PI)

NIAID/NIH

4/15/20-2/28/22

**Supplement to R21: Evaluation of therapeutics targeting SARS-CoV-2 infection and defining pathogenic mechanisms of SARS-CoV-2-triggered pulmonary dysfunction**

Due to the COVID-19 global pandemic, we will expand our current investigation of repurposing FDA-approved cyclodextrins and derivatives from flaviviruses to therapeutics targeting SARS-CoV-2 infection and SARS-Cov-2-mediated vascular permeability. This investigation will also elucidate the molecular mechanism(s) by which the viral spike protein contributes to vascular permeability associated with severe disease.

R01 AI099631 (Harris Co-Investigator; Balmaseda PI)

NIAID/NIH

6/1/17-5/31/22

**Epidemiological, Clinical & Immunological Studies of Zika, dengue and chikungunya**

The main goals of this project are to study epidemiological, clinical and immunological aspects of Zika, dengue, and chikungunya virus infections simultaneously in pediatric populations in Nicaragua; evaluate new, next-generation serological diagnostic assays to differentiate ZIKV and DENV infections; and determine whether clinical or immunological enhancement occurs between DENV and ZIKV and *vice versa*.

U19 AI118626 (Harris Subcontract PI; Sette PD)

NIH/NIAID

6/15/15-5/31/22

**Human immune signatures of Dengue virus and *Mycobacterium tuberculosis* exposure**

The goal of this subcontract is to help supervise the collection, separation, coding and shipping of human peripheral blood mononuclear cells (PBMC) from Nicaraguan blood donors at the Nicaraguan National Blood Center for analysis at the La Jolla Institute for Allergy and Immunology to determine dengue virus-specific signatures in T cells.

825746 RECODID (Harris Subcontract PI, Jaenisch PI)

European Commission

1/1/19-12/31/22

**Integrated human data repositories for infectious disease-related international cohorts to foster personalized medicine approaches to infectious disease research**

The main objective of this project is to build on existing infrastructures and partnerships to develop a sustainable model for the storage, curation, and analyses of the complex data sets collected by infectious disease-related cohorts.